IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BIOVAIL LABORATORIES INTERNATIONAL SRL a corporation of Barbados, Plaintiff, v. ANDRX PHARMACEUTICALS, LLC and ANDRX CORPORATION, Defendants.	)	C.A. Nos. 05-586 (GMS) 05-730 (GMS) 06-620 (GMS) (CONSOLIDATED) **REDACTED - PUBLIC VERSION**

JOINT APPENDIX OF INTRINSIC AND EXTRINSIC EVIDENCE
(VOLUME 2 OF 3)

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Biovail Laboratories International SRL v. Andrx Pharmaceuticals, LLC et al.
U.S.D.C. Del. Case Nos. 05-586, 05-730, 06-620 (GMS) Consolidated

JOINT APPENDIX OF INTRINSIC AND EXTRINSIC EVIDENCE

EXHIBIT 14

RCE/1615

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Our Ref.: PT-1830000

November 22, 2001

Via Courier

Assistant Commissioner for Patents
UNITED STATES PATENT OFFICE
Box RCE
Washington, DC 20231 U.S.A.

Dear Sir:

Re: Request for Continued Examination (RCE)
Application Serial No. 09/567,451, filed on May 8, 2000
of Biovail Laboratories Incorporated
for CHRONOTHERAPEUTIC DILTIAZEM FORMULATIONS AND THE ADMINISTRATION THEREOF
Group Art Unit: 1615 Examiner: A. Pulliam
Due Date: November 25, 2001
CUSTOMER NO. 23607

Please find enclosed herewith the following:

1. Request for Continued Examination (RCE) Transmittal of United States Application Serial No. 09/567,451 under 37 C.F.R. §1.114;

2. Submissions, together with enclosures;

3. Request for a three month extension of time making this response due **November 25, 2001**;

4. Check in the sum of **$1,660.00 U.S.** funds (large entity) to cover the following fees:

   Three month extension of time $920.00 U.S. and base filing fee for a Request for Continued Examination (RCE) $740.00 U.S. If there should occur an overpayment or an underpayment of fees in respect of this submission, the

175 Commerce Valley Dr. W., Suite 200, Thornhill, Ontario, Canada L3T 7P6 Phone: 905 771-6414 Fax: 905 771-6420
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Commissioner is authorized to access Deposit Account Number 08-3255 to make the appropriate adjustments and advise Applicant's agent;

5. Also enclosed herewith is a stamped, self-addressed verification card which we request that you kindly acknowledge and return to this office at the earliest opportunity.

We thank the Patent Office for its cooperation in this regard and look forward to receiving filing data in this matter.

Respectfully submitted,

Ivor M. Hughes
Agent for Applicant
Registration No. 27,759

Marcelo K. Sarkis, P.Eng.
Agent for Applicant
Registration No. 37,015

MKS:mse
Enclosures

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REQUEST FOR CONTINUED EXAMINATION (RCE) TRANSMITTAL

Subsection (b) of 35 U.S.C. § 132, effective on May 29, 2000, provides for continued examination of an utility or plant application filed on or after June 8, 1995.
See The American Inventors Protection Act of 1999 (AIPA).

Application Number	09/567,451
Filing Date	May 8, 2000
First Named Inventor	Kenneth S. Albert
Group Art Unit	1615
Examiner Name	Amy E. Pulliam
Attorney Docket Number	PT-1830000

This is a Request for Continued Examination (RCE) under 37 C.F.R. § 1.114 of the above-identified application.

NOTE: 37 C.F.R. § 1.114 is effective on May 29, 2000. If the above-identified application was filed prior to May 29, 2000, applicant may wish to consider filing a continued prosecution application (CPA) under 37 C.F.R. § 1.53 (d) (PTO/SB/29) instead of a RCE to be eligible for the patent term adjustment provisions of the AIPA. See Changes to Application Examination and Provisional Application Practice, Final Rule, 65 Fed. Reg. 50092 (Aug. 16, 2000); Interim Rule, 65 Fed. Reg. 14865 (Mar. 20, 2000), 1233 Off. Gaz. Pat. Office 47 (Apr. 11, 2000), which established RCE practice.

Ref
11-28-01

1. Submission required under 37 C.F.R. § 1.114
   - a. [ ] Previously submitted
     - i. [ ] Consider the amendment(s)/reply under 37 C.F.R. § 1.116 previously filed on _____ (Any unentered amendment(s) referred to above will be entered).
     - ii. [ ] Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
     - iii. [ ] Other _____
   - b. [X] Enclosed
     - i. [X] Amendment/Reply
     - ii. [ ] Affidavit(s)/Declaration(s)
     - iii. [ ] Information Disclosure Statement (IDS)
     - iv. [ ] Other _____
2. Miscellaneous
   - a. [ ] Suspension of action on the above-identified application is requested under 37 C.F.R. § 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 C.F.R. § 1.17(i) required)
   - b. [ ] Other _____
3. Fees — The RCE fee under 37 C.F.R. § 1.17(e) is required by 37 C.F.R. § 1.114 when the RCE is filed.
   - a. [X] The Director is hereby authorized to ~~charge the following fees~~ or credit any overpayments, to Deposit Account No. 08-3255
     - i. [X] RCE fee required under 37 C.F.R. § 1.17(e)
     - ii. [X] Extension of time fee (37 C.F.R. §§ 1.136 and 1.17)
     - iii. [ ] Other _____
   - b. [X] Check in the amount of $ 1,660.00 USD enclosed
   - c. [ ] Payment by credit card (Form PTO-2038 enclosed)

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Name (Print/Type)	Marcelo K. Sarkis, P.Eng.	Registration No. (Attorney/Agent)	37,015
Signature		Date	November 22, 2001

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner For Patents, Box RCE, Washington, DC 20231, or facsimile transmitted to the U.S. Patent and Trademark Office on:

Name (Print/Type)			
Signature		Date	

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND Fees and Completed Forms to the following address: Assistant Commissioner for Patents, Box RCE, Washington, DC 20231.

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IN THE UNITED STATES PATENT OFFICE

Application Serial No. 09/567,451

Our Ref.: PT1830000
CUSTOMER NO. 23607

Applicant: Biovail Laboratories Incorporated

Agent: Ivor M. Hughes
Barrister & Solicitor
Patent & Trade Mark Agents
Suite 200
175 Commerce Valley Drive West
Thornhill, Ontario
Canada L3T 7P6

Title: CHRONOTHERAPEUTIC DILTIAZEM FORMULATIONS AND THE ADMINISTRATION THEREOF

Inventors: Kenneth S. Albert
Paul José Maes

Examiner: Amy E. Pulliam

Group Art Unit: 1615

Filing Date: May 8, 2000

Due Date: November 25, 2001

SUBMISSIONS ACCOMPANYING REQUEST FOR CONTINUED EXAMINATION (RCE)

November 22, 2001

The Commissioner of Patents
UNITED STATES PATENT OFFICE
2011 South Clark Place
Crystal Plaza 2, Room 1B03
Arlington, Virginia, U.S.A. 22202

Dear Sir:

Applicant respectfully requests that the following submissions for a Continued Examination (RCE) be entered as a Response to the Examiner's Action dated May 25, 2001 and due for response August 25, 2001 finally rejecting claims 1 to 43, 45 to 51, 53 to 63, 65 to 105, 107 to 113, 115 to 125, 127 and 128. The required fee

in the amount of $740.00 USD in payment of the base filing fee for a Request for Continued Examination (RCE) for a large entity is enclosed.

Applicant also encloses a Request for a three month extension of time with the fee for a large entity of **$920.00 U.S.** funds making this response due **November 25, 2001.** Since November 25, 2001 falls on a Sunday, the due date is extended to Monday, November 26, 2001. If there is any deficiency or surplusage of the fees enclosed for the Extension of Time, please obtain any such deficiency or credit the surplusage to Deposit Account 08-3255 and advise Applicant's Agent.

IN THE ABSTRACT

No changes.

IN THE DISCLOSURE

No changes.

IN THE CLAIMS

Applicant respectfully requests the following amendments be made to the claims. No new subject matter has been added to the application.

52. (Twice Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-

release dosage form in which the Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans (i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and (ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose (Avicel ph101)	8 - 9.5
(c)	Povidone K30 (Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween) (Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025
(j)	Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing)

64. (Twice Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120

mg to about 540 mg (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans

(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and

(ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria, in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

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(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants,

wherein the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose (Avicel ph101)	8 - 9.5
(c)	Povidone K30 (Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate (crodesta F150)	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween) (Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025
(j)	Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing).

[67. A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the

form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;
(b) between about 7% and about 35% after 4 hours;
(c) between about 30% and about 58% after 8 hours;
(d) between about 55% and about 80% after 14 hours; and
(e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;
(b) between about 7% and about 45% after about 4 hours;
(c) between about 30% and about 68% after about 8 hours;
(d) in excess of about 75% after about 24 hours.]

[68. A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;
(b) between about 16% and about 21% after 4 hours;
(c) between about 44% and about 52% after 8 hours;
(d) between about 69% and about 76% after 14 hours; and
(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;
(b) between about 16% and about 30% after 4 hours;
(c) between about 44% and about 62% after 8 hours;
(d) in excess of about 80% after 24 hours.]

[69. The preparation of claim 68 wherein the Cmax of Diltiazem in the blood is obtained between about 11 - about 13 hours after administration of the preparation.]

[70. The preparation of claim 68 wherein the Diltiazem is in the form of Diltiazem HCl.]

[71. The preparation of claim 68 wherein the preparation is a diffusion controlled preparation.]

[72. The preparation of claim 68 wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution.]

[73. The preparation of claim 68 in capsule form.]

[74. The preparation of claim 68 in tablet form.]

[75. The preparation of claim 67 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.]

[76. The preparation of claim 75 wherein the Diltiazem is mixed (in whole or in part) with the wetting agent.]

[77. The preparation of claim 76 wherein the wetting agent assists to maintain the solubility of the Diltiazem in each microgranule, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.]

[78. The preparation of claim 77 wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.]

[79. The preparation of claim 75 wherein the preparation comprises a mixture of the Diltiazem and/or pharmaceutically acceptable salt with the wetting agent and the membrane comprises a water-dispersible or water-soluble polymer (such as HPMC) and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.]

[80. The preparation of claim 77 wherein the membrane comprises Eudragit NE30D and hydroxypropylmethylcellulose.]

[81. The preparation of claim 80 wherein the membrane hydrates the core within a membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the microgranule, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).]

[82. The preparation of claim 77 wherein the Diltiazem is mixed with the wetting agent and the membrane comprises an acrylic polymer and plasticizer combined to form the membrane thereby providing a mechanism of release from this membrane which "washes" the diltiazem through pores created when the plasticizer incorporated in the membrane, is released in gastrointestinal fluid.]

[83. The preparation of claim 68 wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or a pharmaceutically acceptable salt thereof associated with any suitable dissolution agent (other than a wetting agent) to assist in the release of the Diltiazem from the preparation.]

[84. The preparation of claim 83 wherein the dissolution agent is an organic acid comprising adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid or tartaric acid which permits the diltiazem to dissolve in gastrointestinal fluids when the microgranules pass into the regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble.]

[85. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 67 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[86. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 68 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[87. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 69 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[88. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 70 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[89. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 71 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[90. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 72 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[91. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 73 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[92. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 74 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[93. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 75 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[94. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 76 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[95. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 77 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[96. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 78 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[97. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 79 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[98. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 80 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[99. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 81 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[100. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 82 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[101. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 83 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[102. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 84 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[103. The preparation of claim 68 wherein the preparation contains 120 mg of Diltiazem.]

[104. The preparation of claim 68 wherein the preparation contains 180 mg of Diltiazem.]

[105. The preparation of claim 68 wherein the preparation contains 240 mg of Diltiazem.]

[106. The preparation of claim 68 wherein the preparation contains 300 mg of Diltiazem.]

[107. The preparation of claim 68 wherein the preparation contains 360 mg of Diltiazem.]

[108. The preparation of claim 68 wherein the preparation contains 420 mg of Diltiazem.]

[109. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 103, 104, 105, 106, 107 or 108 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[111. The preparation of claim 75 wherein the wetting agent is in association with the diltiazem in the microgranule and not mixed therewith, the membrane comprises a water-soluble or water dispersible polymer or copolymer such as hydroxypropylmethylcellulose and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester enabling the bead to be hydrated by the introduction of intestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.]

114. (Twice Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours

(Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;

(b) between about 16% and about 21% after 4 hours;

(c) between about 44% and about 52% after 8 hours;

(d) between about 69% and about 76% after 14 hours; and

(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose	8 - 9.5
(c)	Povidone K30 (Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0

(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween) (Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025
(j)	Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing)

Ep note

[120. The preparation of claim 77 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.]

[121. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 120 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

126. (Amended) The preparation of claim 122, 123 or 124 wherein the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose (Avicel ph101)	8 - 9.5
(c)	Povidone K30 (Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate (crodesta F150)	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3

(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween)	0.01 - 0.025
	(Polyoxyethylene Sorbitan Monooleate)	
(j)	Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	Eudragit NE30 D (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing).

REMARKS

Applicant would like to acknowledge the claims that have been allowed by the Examiner, namely claims 44, 106 and 114. Claims 52, 64, and 126 would be allowable if rewritten or amended to overcome the rejections under 35 USC 112, 2nd paragraph. Applicant has amended claims 52, 64 and 126 in order to clarify the invention and in doing so also overcomes the rejections under 35 USC 112, 2nd paragraph. Therefore claims 52, 64 and 126 should be in allowable condition. Claims 67 to 109, 111, 120 and 121 have been cancelled.

Claims 1 to 66, 110, 112 to 119, 122 to 128 remain in the application. In order to accelerate the prosecution of this application, the purported overlapping claims as indicated by the Examiner have been cancelled in this application.

The Examiner has in effect allowed the 300 mg dosage form as providing unexpected utility over the prior art based on the submissions in the last response filed on May 01, 2001. The Examiner, having concluded that Claim 40 contains allowable subject matter, must have accepted the data provided in our last response. As the Examiner will recall, she cited EPA 856 313 ('313) and WO 93/00 093 ('093) (Goeghegan and Deboeck, respectively) against the application in rejections based on anticipation and obviousness. The Examiner, at page 6 of the last Official Action, with respect to the EPA '313, stated:

> Additionally, applicant has submitted data, and claims unexpected results in order to overcome the rejection under 35 U.S.C. 103(a). The examiner has thoroughly considered the submitted data and declarations, and finds them to be persuasive only for a 300 mg capsule, as that is the only dosage form discussed in the comparison. Excluding claim 40, none of the above rejected claims are commensurate in scope with the data provided.

With respect to WO '093, the Examiner stated as follows:

> Furthermore, applicant argues that the peak to trough variance for the WO '093 reference (which corresponds to Tiazac) is much larger than that of applicant's formulation. Applicant has provided evidence to reinforce this statement. However, the examiner respectfully disagrees as the data regarding Tiazac is concerning a 240 mg formulation, and the data regarding applicant's claimed formulation is based on a 300 mg capsule. Therefore, this comparison is not persuasive, and the rejection is maintained.

It is therefore clear that with appropriate data and submissions, the Examiner would be prepared to consider the allowability of the other dosage form claims.

With respect to the other dosage forms, Applicant submits that for the same reasons the Examiner has indicated the allowability of the claims in respect of the 300 mg dosage form, the Examiner should allow the claims in respect of all the dosage forms. The bases are – scientific analysis and determination and Pharmacokinetic testing.

The Examiner will recall that submissions were made by Applicant in respect of "Peak to Trough Variation". This characteristic is also identified as the "Degree of Fluctuation". The "Degree of Fluctuation" can be determined both scientifically by analyzing data in accordance with scientific principles and calculations and by testing, both pharmacokinetic and clinical.

1) Scientific demonstration:

The Degree of Fluctuation (% Fluct.) is a true measure of the "Peak to Trough Variation". The % Fluct. is a common measure obtained from Pharmacokinetic

studies called Biovailaibility or bioequivalence studies; it can also be computed using FDA's scientific criteria for determining the Degree of Fluctuation (% Fluct.). See Schedule 1. (Schedule 1 - %Fluct.) This calculation or determination is based on the difference between the Maximal Plasma concentration (Cmax.) and the Minimum plasma concentration (Cmin.) divided by the average concentration during dosing interval. According to the scientific community, the Degree of Fluctuation should be determined in accordance with Schedule 2 (Schedule 2 =%Swing) using the better and more accurate formula (and preferred formula where the maximal plasma level difference is divided by the Cmin). The Examiner will appreciate that when solving the equations (both in Schedules 1 and 2) and substituting for known elements, when solving the equation for determining "Degree of Fluctuation" (Peak to Trough Variation) is DOSE INDEPENDENT. The Degree of Fluctuation is dependent only on absorption and elimination rates (contributed by the characteristics of the dosage) and the dosing interval but not the dose itself.

The two Schedules (1 and 2) represent a mathematical demonstration of the determination that there is no Dose factor in determining the % Fluct. from the equations. (The basic pharmacokinetic equations were extracted from the Reference Book edited by Milo Gibaldi and Donald Perrier in 1976 (excerpt attached as Schedule 3).)

The Examiner will therefore now appreciate why Applicant submitted that the earlier submissions applied to all of the dosages claimed herein.

2) Pharmacokinetic Test Results

To assist the Examiner further, Applicant encloses the results of a Steady State Pharmacokinetic dose ranging study. (See Schedule 4: Study #1821.) Unlike other commonly measured parameters such as AUC (Area Under The Curve) and Cmax

(Maximal Concentration), the % Fluct. for the dosages as confirmed by these results remains constant (within experimental limits).

The Diltiazem % Fluct. found were respectively, 114.74% for the 120 mg strength, 108.23% for the 240 mg strength and 114.55% for the 300 mg strength of Diltiazem. These values are consistent with both the scientific calculations (both FDA's calculations and the scientific community's calculations).

As expected the same conclusion is also reached for the active metabolites Deacetyldiltiazem and Desmethyldiltiazem. (See also Schedule 4.) It is therefore clear that the science confirms the Pharmacokinetics and the Pharmacokinetic testing confirms the science.

Therefore, in light of the above, none of the claims currently of record are anticipated nor obviated by the prior art of record. Thus reconsideration of the claims is respectfully requested.

Attached hereto as **Exhibit A** is a marked-up version of the changes made to the claims by the present amendment. Exhibit A is entitled "EXHIBIT A - CLAIMS WITH MARKINGS TO SHOW CHANGES".

Attached hereto as **Exhibit B** is a clean set of all pending claims following entry of this amendment. Exhibit B is entitled: "EXHIBIT B - CLEAN SET OF ALL PENDING CLAIMS FOLLOWING ENTRY OF THE PRESENT AMENDMENT". All of the currently pending claims are consolidated in this list for the convenience of the Examiner.

Applicants have enclosed one cheque in the sum of **$1,660.00 U.S.** which incorporates the fee of $920.00 U.S. for the three month extension of time and $740.00 U.S. for filing the Request for Continued Examination (RCE). If there is any deficiency or surplusage of the fees enclosed for the Extension of Time, please obtain

any such deficiency or credit the surplusage to Deposit Account 08-3255 and advise Applicant's Agent.

In view of the above submissions, Applicant respectfully submits that the Application is in condition for allowance and same is solicited at the earliest convenience.

Once the Examiner has received and examined the Request for Continued Examination (RCE) and Submission, Applicant's agent requests that the Examiner contact Applicant's Agent, Ivor M. Hughes, or Marcelo K. Sarkis, at (905) 771-6414 (collect) at the Examiner's convenience.

Respectfully submitted,

Ivor M. Hughes
Registration #27,759
Agent for Applicant

Marcelo K. Sarkis, P.Eng.
Registration #37,015
Agent for Applicant

IMH/mse
Enclosures
1. Exhibit A (Pending Claims with Markings);
2. Exhibit B (Clean Set of Pending Claims);
3. Schedule 1;
4. Schedule 2;
5. Schedule 3;
6. Schedule 4;
7. Requisition for a Three-Month Extension of Time;
8. Cheque in the amount of $1,660.00 USD

Application Serial No. 09/567,451
Group Art Unit 1615

EXHIBIT A
CLAIMS WITH MARKINGS TO SHOW CHANGES

52. (Twice Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans

(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and

(ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose (Avicel ph101)	8 - 9.5
(c)	Povidone K30 (Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3

(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween) (Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025
(j)	Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing)

64. (Twice Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans

(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and

(ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria, in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants,

wherein the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose (Avicel ph101)	8 - 9.5
(c)	Povidone K30 (Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate (crodesta F150)	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween)	0.01 - 0.025

	(Polyoxyethylene Sorbitan Monooleate)	
(j)	Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing).

[67. A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;
(b) between about 7% and about 35% after 4 hours;
(c) between about 30% and about 58% after 8 hours;
(d) between about 55% and about 80% after 14 hours; and
(e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;
(b) between about 7% and about 45% after about 4 hours;
(c) between about 30% and about 68% after about 8 hours;

(d) in excess of about 75% after about 24 hours.]

[68. A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;
(b) between about 16% and about 21% after 4 hours;
(c) between about 44% and about 52% after 8 hours;
(d) between about 69% and about 76% after 14 hours; and
(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;
(b) between about 16% and about 30% after 4 hours;
(c) between about 44% and about 62% after 8 hours;
(d) in excess of about 80% after 24 hours.]

[69. The preparation of claim 68 wherein the Cmax of Diltiazem in the blood is obtained between about 11 - about 13 hours after administration of the preparation.]

[70. The preparation of claim 68 wherein the Diltiazem is in the form of Diltiazem HCl.]

[71. The preparation of claim 68 wherein the preparation is a diffusion controlled preparation.]

[72. The preparation of claim 68 wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution.]

[73. The preparation of claim 68 in capsule form.]

[74. The preparation of claim 68 in tablet form.]

[75. The preparation of claim 67 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.]

[76. The preparation of claim 75 wherein the Diltiazem is mixed (in whole or in part) with the wetting agent.]

[77. The preparation of claim 76 wherein the wetting agent assists to maintain the solubility of the Diltiazem in each microgranule, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.]

[78. The preparation of claim 77 wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer

of a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.]

[79. The preparation of claim 75 wherein the preparation comprises a mixture of the Diltiazem and/or pharmaceutically acceptable salt with the wetting agent and the membrane comprises a water-dispersible or water-soluble polymer (such as HPMC) and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.]

[80. The preparation of claim 77 wherein the membrane comprises Eudragit NE30D and hydroxypropylmethylcellulose.]

[81. The preparation of claim 80 wherein the membrane hydrates the core within a membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the microgranule, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).]

[82. The preparation of claim 77 wherein the Diltiazem is mixed with the wetting agent and the membrane comprises an acrylic polymer and plasticizer combined to form the membrane thereby providing a mechanism of release from this membrane which "washes" the diltiazem through pores created when the plasticizer incorporated in the membrane, is released in gastrointestinal fluid.]

[83. The preparation of claim 68 wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or a pharmaceutically acceptable salt thereof associated with any suitable dissolution agent (other than a wetting agent) to assist in the release of the Diltiazem from the preparation.]

[84. The preparation of claim 83 wherein the dissolution agent is an organic acid comprising adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid or tartaric acid which permits the diltiazem to dissolve in gastrointestinal fluids when the microgranules pass into the regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble.]

[85. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 67 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[86. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 68 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[87. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 69 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[88. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 70 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[89. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 71 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[90. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 72 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[91. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 73 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[92. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 74 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[93. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 75 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[94. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 76 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[95. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 77 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[96. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 78 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[97. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 79 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[98. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 80 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[99. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 81 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[100. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 82 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[101. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 83 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[102. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 84 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[103. The preparation of claim 68 wherein the preparation contains 120 mg of Diltiazem.]

[104. The preparation of claim 68 wherein the preparation contains 180 mg of Diltiazem.]

[105. The preparation of claim 68 wherein the preparation contains 240 mg of Diltiazem.]

[106. The preparation of claim 68 wherein the preparation contains 300 mg of Diltiazem.]

[107. The preparation of claim 68 wherein the preparation contains 360 mg of Diltiazem.]

[108. The preparation of claim 68 wherein the preparation contains 420 mg of Diltiazem.]

[109. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 103, 104, 105, 106, 107 or 108 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

[111. The preparation of claim 75 wherein the wetting agent is in association with the diltiazem in the microgranule and not mixed therewith, the membrane comprises a water-soluble or water dispersible polymer or copolymer such as

hydroxypropylmethylcellulose and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester enabling the bead to be hydrated by the introduction of intestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.]

114. (Twice Amended) A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;

(b) between about 16% and about 21% after 4 hours;

(c) between about 44% and about 52% after 8 hours;

(d) between about 69% and about 76% after 14 hours; and

(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core

containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose	8 - 9.5
(c)	Povidone K30 (Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween) (Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025
(j)	Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing)

[120. The preparation of claim 77 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.]

[121. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 120 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.]

126. (Amended) The preparation of claim 122, 123 or 124 wherein the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose (Avicel ph101)	8 - 9.5
(c)	Povidone K30 (Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate (crodesta F150)	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween) (Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025
(j)	Simethicone C emulsion USP (dry.of 30%)	0.01 - 0.015
(k)	Eudragit NE30 D (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing).

Application Serial No. 09/567,451
Group Art Unit 1615

EXHIBIT B
CLEAN SET OF ALL PENDING CLAIMS FOLLOWING ENTRY OF THE PRESENT AMENDMENT

1. A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans

(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and

(ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria.

2. The controlled release Galenical preparation of claim 1 wherein the higher bioavailability achieved after night administration of the preparation than morning administration without food exceeds 25% C_{max}.

3. A method of treatment of a patient's hypertension and/or angina comprising administration of a preparation of claim 1 in the night to a patient for effect the next morning and which formulation exhibits a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and bioequivalence when given with food and without food according to the same FDA guidelines or criteria.

4. The controlled-release Galenical preparation of claim 1 wherein the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;
(b) between about 7% and about 35% after 4 hours;
(c) between about 30% and about 58% after 8 hours;
(d) between about 55% and about 80% after 14 hours; and
(e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;
(b) between about 7% and about 45% after about 4 hours;
(c) between about 30% and about 68% after about 8 hours;
(d) in excess of about 75% after about 24 hours.

5. The controlled-release Galenical preparation of claim 2 in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;
(b) between about 16% and about 21% after 4 hours;
(c) between about 44% and about 52% after 8 hours;
(d) between about 69% and about 76% after 14 hours; and
(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours.

6. The preparation of claim 4 wherein the Cmax of Diltiazem in the blood is obtained between about 11 - about 13 hours after administration of the preparation.

7. The preparation of claim 1, 2, 4, 5 or 6 wherein the Diltiazem is in the form of Diltiazem HCl.

8. The preparation of claim 6 wherein the preparation is a diffusion controlled preparation.

9. The preparation of claim 5 wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution.

10. The preparation of claim 9 in capsule form.

11. The preparation of claim 9 in tablet form.

12. The preparation of claim 9 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

13. The preparation of claim 12 wherein the Diltiazem is mixed (in whole or in part) with the wetting agent.

14. The preparation of claim 13 wherein the wetting agent assists to maintain the solubility of the Diltiazem in each microgranule, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

15. The preparation of claim 14 wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

16. The preparation of claim 12 wherein the preparation comprises a mixture of the Diltiazem and/or pharmaceutically acceptable salt with the wetting agent and the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

17. The preparation of claim 16 wherein the membrane comprises a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester and hydroxypropylmethylcellulose.

18. The preparation of claim 17 wherein the membrane hydrates the core within a membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the microgranule, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

19. The preparation of claim 13 wherein the Diltiazem is mixed with the wetting agent and the membrane comprises an acrylic membrane and plasticizer combined

to form the membrane thereby providing a mechanism of release from this membrane which "washes" the diltiazem through pores created when the plasticizer incorporated in the membrane, is released in gastrointestinal fluid.

20. The preparation of claim 9 wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or a pharmaceutically acceptable salt thereof associated with any suitable dissolution agent (other than a wetting agent) to assist in the release of the Diltiazem from the preparation.

21. The preparation of claim 20 wherein the dissolution agent is an organic acid comprising adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid or tartaric acid which permits the diltiazem to dissolve in gastrointestinal fluids even when the microgranules pass into the regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble.

22. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 1 or 2 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

23. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 4 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

24. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 5 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

25. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 6 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

26. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 7 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

27. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 8 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

28. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 9 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

29. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 10 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

30. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 11 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

31. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 12 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

32. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 13 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

33. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 14 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

34. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 15 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

35. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 16 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

36. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 17 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

37. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 18 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

38. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 19 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

39. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 20 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

40. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 21 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

41. The preparation of claim 5 wherein the preparation contains 120 mg of Diltiazem.

42. The preparation of claim 5 wherein the preparation contains 180 mg of Diltiazem.

43. The preparation of claim 5 wherein the preparation contains 240 mg of Diltiazem.

44. The preparation of claim 5 wherein the preparation contains 300 mg of Diltiazem.

45. The preparation of claim 5 wherein the preparation contains 360 mg of Diltiazem.

46. The preparation of claim 5 wherein the preparation contains 420 mg of Diltiazem.

47. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 41, 42, 43, 44, 45 or 46 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

48. The preparation of claim 17 wherein the wetting agent is selected from:

sugars;
saccharose, mannitol, sorbitol;
lecithins;
C_{12} to C_{20} fatty acid esters of saccarose, including sucrose stearate;
xylose esters or xylites;
polyoxyethylenic glycerrides;
esters of fatty acids and polyoxyethylene;
sorbitan fatty acid ester;
polyglycides-glycerides and polyglycides-alcohols esters
Metal salts.

49. The preparation of claim 12 wherein the wetting agent is in association with the diltiazem in the microgranule and not mixed therewith, the membrane comprises a water-soluble or water dispersible polymer or copolymer such as hydroxypropylmethylcellulose and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester

enabling the bead to be hydrated by the introduction of intestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.

50. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 48 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

51. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 49 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

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52. A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans

(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and

(ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose (Avicel ph101)	8 - 9.5
(c)	Povidone K30 (Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween) (Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025
(j)	Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing)

53. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 48 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

54. The preparation of claim 12 in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

55. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 54 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

56. The preparation of claim 12 in which the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

57. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 56 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

58. The preparation of claim 12 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.

59. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 58 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

60. The controlled-release Galenical preparation of claim 2 in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises

Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

61. The preparation of claim 60 wherein the microgranules are in capsule form.

62. The preparation of claim 60 wherein the microgranules are in tablet form.

63. The preparation of claim 60 wherein the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

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64. A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg (as desired) of the form of Diltiazem associated with excipients to provide controlled (sustained) release of the form of Diltiazem for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the Diltiazem is adapted to be released after administration over a prolonged period of time and exhibits when given to humans

(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and

(ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria, in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants,

wherein the core and membrane comprise:

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		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose (Avicel ph101)	8 - 9.5
(c)	Povidone K30 (Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate (crodesta F150)	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween) (Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025
(j)	Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing).

65. The preparation of claim 60 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.

66. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 60 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

110. A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the

form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;

(b) between about 16% and about 21% after 4 hours;

(c) between about 44% and about 52% after 8 hours;

(d) between about 69% and about 76% after 14 hours; and

(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the wetting agent is selected from:

sugars;

saccharose, mannitol, sorbitol;

lecithins;

C_{12} to C_{20} fatty acid esters of saccarose, commercialized under the name of sucroesters or under the name of crodesters such as sucrose stearate marketed under the trade name of Crodesta;
xylose esters or xylites;
polyoxyethylenic glycerrides;
esters of fatty acids and polyoxyethylene;
sorbitan fatty acid esters;
polyglycides-glycerides and polyglycides-alcohols esters
Metal salts.

112. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 110 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

113. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 111 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

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114. A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;

(b) between about 16% and about 21% after 4 hours;

(c) between about 44% and about 52% after 8 hours;

(d) between about 69% and about 76% after 14 hours; and

(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose	8 - 9.5
(c)	Povidone K30 (Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween) (Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025
(j)	Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015

(k)	neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing)

115. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 112 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

116. A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;
(b) between about 16% and about 21% after 4 hours;
(c) between about 44% and about 52% after 8 hours;
(d) between about 69% and about 76% after 14 hours; and
(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

117. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 116 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

118. A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;

(b) between about 16% and about 21% after 4 hours;

(c) between about 44% and about 52% after 8 hours;

(d) between about 69% and about 76% after 14 hours; and

(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core

containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

C10 cont

119. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 118 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

122. A controlled-release Galenical preparation of pharmaceutically acceptable Diltiazem including the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

123. The preparation of claim 122 wherein the microgranules are in capsule form.

124. The preparation of claim 122 wherein the microgranules are in tablet form.

125. The preparation of claim 122, 123 or 124 wherein the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

126. The preparation of claim 122, 123 or 124 wherein the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose (Avicel ph101)	8 - 9.5
(c)	Povidone K30 (Polyvinyl Pyrrolidone)	1 - 2
(d)	Sucrose stearate (crodesta F150)	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween) (Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025
(j)	Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	Eudragit NE30 D (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing).

127. The preparation of claim 122 or 124 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.

128. A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 122, 123 or 124 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

SCHEDULE 1

$$\textbf{Degree of Fluctuation} = \frac{C^{ss}_{max} - C^{ss}_{min}}{C_{avg}} * 100\,\%$$

Where

$$C^{ss}_{max} = \frac{FDose}{V_d}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-kt'_p}, \quad \text{with } t'_p = 2.303 * \log\left(\frac{k_a(1-e^{-k\tau})/k(1-e^{-k_a\tau})}{k_a - k}\right)$$

$$C^{ss}_{min} = \frac{k_a FDose}{V_d(k_a - k)}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-k\tau}$$

$$C_{avg} = \frac{AUC_\tau}{\tau}, \quad \text{with } AUC_\tau = \frac{FDose}{Cl}$$

$$\text{Since } Cl = kV_d \rightarrow AUC_\tau = \frac{FDose}{kV_d}$$

$$\text{Therefore } C_{avg} = \frac{\left(\frac{FDose}{kV_d}\right)}{\tau}$$

F = Fraction Absorbed
k_a = Absorption Rate Constant
k = Elimination Rate Constant
V_d = Apparent Volume of Distribution
Cl = Clearance
τ = Dosing Interval

By substituting the above C^{ss}_{max}, C^{ss}_{min} and C_{avg} equations into the Degree of Fluctuation equation:

$$\textbf{Degree of Fluctuation} = \frac{\left(\frac{FDose}{V_d}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-kt'_p}\right) - \left(\frac{k_a FDose}{V_d(k_a - k)}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-k\tau}\right)}{\frac{\left(\frac{FDose}{kV_d}\right)}{\tau}} * 100\,\%$$

Simplifying the equation →

$$\frac{\frac{FDose}{V_d}\left[\left(\frac{1}{1-e^{-k\tau}}\right)e^{-kt'_p}-\left(\frac{k_a}{(k_a-k)}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-k\tau}\right)\right]}{\frac{FDose}{V_d}\left(\frac{1}{k\tau}\right)} * 100\ \%$$

Then cancelling out the term $\frac{FDose}{V_d}$ →

$$\frac{\left(\frac{1}{1-e^{-k\tau}}\right)e^{-kt'_p}-\left(\frac{k_a}{(k_a-k)}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-k\tau}\right)}{\left(\frac{1}{k\tau}\right)} * 100\ \%$$

Finally, rearranging the equation further →

$$\frac{\frac{1}{1-e^{-k\tau}}\left(e^{-kt'_p}-\frac{k_a}{(k_a-k)}e^{-k\tau}\right)}{\left(\frac{1}{k\tau}\right)} * 100\ \%$$

∴ **Degree of Fluctuation** =

$$\frac{\frac{1}{1-e^{-k\tau}}\left(e^{-kt'_p}-\frac{k_a}{(k_a-k)}e^{-k\tau}\right)}{\left(\frac{1}{k\tau}\right)} * 100\ \%$$

CONCLUSION:

- **Degree of Fluctuation is dose independent**
- **Degree of Fluctuation is dependent on absorption and elimination rates and the dosing interval**

SCHEDULE 2

$$\textbf{Degree of Fluctuation} = \frac{C^{ss}_{max} - C^{ss}_{min}}{C^{ss}_{min}} * 100\,\%$$

Where

$$C^{ss}_{max} = \frac{FDose}{V_d}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-kt'_p}, \quad \text{with } t'_p = 2.303 * \log\frac{k_a(1-e^{-k\tau})/k(1-e^{-k_a\tau})}{k_a - k}$$

$$C^{ss}_{min} = \frac{k_a FDose}{V_d(k_a - k)}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-k\tau}$$

F = Fraction Absorbed
k_a = Absorption Rate Constant
k = Elimination Rate Constant
V_d = Apparent Volume of Distribution
τ = Dosing Interval

By substituting the above C^{ss}_{max} and C^{ss}_{min} equations into the Degree of Fluctuation equation:

$$\textbf{Degree of Fluctuation} = \frac{\left(\frac{FDose}{V_d}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-kt'_p}\right) - \left(\frac{k_a FDose}{V_d(k_a-k)}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-k\tau}\right)}{\frac{k_a FDose}{V_d(k_a-k)}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-k\tau}} * 100\,\%$$

$$\rightarrow \frac{\frac{FDose}{V_d}\left[\left(\frac{1}{1-e^{-k\tau}}\right)e^{-kt'_p} - \left(\frac{k_a}{(k_a-k)}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-k\tau}\right)\right]}{\frac{FDose}{V_d}\left(\frac{k_a}{(k_a-k)}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-k\tau}\right)} * 100\,\%$$

By canceling out the term $\frac{FDose}{V_d}$ $\rightarrow$ $\frac{\left(\frac{1}{1-e^{-k\tau}}\right)e^{-kt'_p} - \left(\frac{k_a}{(k_a-k)}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-k\tau}\right)}{\frac{k_a}{(k_a-k)}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-k\tau}} * 100\,\%$

Rearranging the equation further →

$$\frac{\frac{1}{1-e^{-kr}}\left(e^{-kt'_p}-\frac{k_a}{(k_a-k)}e^{-kr}\right)}{\frac{1}{1-e^{-kr}}\left(\frac{k_a}{(k_a-k)}e^{-kr}\right)} * 100\,\%$$

Finally, by cancelling out the term $\frac{1}{1-e^{-kr}}$ →

$$\frac{\left(e^{-kt'_p}-\frac{k_a}{(k_a-k)}e^{-kr}\right)}{\left(\frac{k_a}{(k_a-k)}e^{-kr}\right)} * 100\,\%$$

∴ **Degree of Fluctuation** =

$$\frac{\left(e^{-kt'_p}-\frac{k_a}{(k_a-k)}e^{-kr}\right)}{\left(\frac{k_a}{(k_a-k)}e^{-kr}\right)} * 100\,\%$$

CONCLUSION:

- **Degree of Fluctuation is dose independent**
- **Degree of Fluctuation is dependent on absorption and elimination rates and the dosing interval**

SCHEDULE 3

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Chapter 3

MULTIPLE DOSING

Some drugs, e.g., analgesics, hypnotics, neuromuscular blocking agents, bronchodilators, and antiemetics, may be used effectively as a single dose. More frequently, drugs are given on a continuous basis. Moreover, most drugs are administered with sufficient frequency that measureable and, often, pharmacologically significant, levels of drug persist in the body when a subsequent dose is administered. For drugs administered in a fixed dose at a constant dosing interval, e.g., every 6 hr or once a day, the peak plasma level following the second and succeeding doses of a drug is higher than the peak level after the first dose, and therefore the drug accumulates in the body relative to the initial dose. However, under these conditions drug accumulation proceeds at a decreasing rate with increasing number of doses until a steady-state plasma level of drug is achieved. At steady state, the plasma concentration of drug at any point in time during any dosing interval will be identical. As will be demonstrated, the rate and extent of accumulation of a drug is a function of the relative magnitudes of the dosing interval and the half-life of the drug. A model-independent approach to multiple dosing is discussed in Appendix 5.

I. ONE-COMPARTMENT MODEL

A. Intravenous Injection

Following the intravenous injection of a drug, the maximum amount of drug in the body $(X_1)_{max}$ would equal the dose X_0, that is,

$$(X_1)_{max} = X_0 \tag{341}$$

As illustrated in Chap. 1, the amount of drug in the body X as a function of time t for a drug that confers one-compartment characteristics to the body following rapid intravenous injection may be described by

$$X = X_0 e^{-Kt} \tag{5}$$

where K is the apparent first-order elimination rate constant of the drug and is related to the half-life of the drug ($t_{\frac{1}{2}} = 0.693/K$). Therefore, the amount of drug in the body at the end of a dosing interval of length τ time units will be given by the relationship

$$X = X_0 e^{-K\tau} \tag{342}$$

Since the amount of drug in the body at the end of a dosing interval (i.e., immediately prior to the administration of a second dose) is a minimum (Fig. 3-1), Eq. (342) may be written as

$$(X_1)_{min} = X_0 e^{-K\tau} \tag{343}$$

where $(X_1)_{min}$ is the minimum amount of drug in the body after the first dose.

Administration of a second dose, equal in size to the first dose, would produce an immediate increase in the body levels of drug yielding a new maximum $(X_2)_{max}$ which would be equal to the sum of the amount of drug in the body at the time of administration (i.e., at time $t = \tau$) and the administered dose. Therefore,

$$(X_2)_{max} = X_0 + (X_1)_{min} = X_0(1 + e^{-K\tau}) \tag{344}$$

where $(X_1)_{min}$ is given by (343). The minimum amount of drug in the body after the second dose $(X_2)_{min}$ (assuming a constant dosing interval of τ) is given by

$$(X_2)_{min} = (X_2)_{max} e^{-K\tau} = X_0(1 + e^{-K\tau})e^{-K\tau} \tag{345}$$

which can be modified to yield

$$(X_2)_{min} = X_0(e^{-K\tau} + e^{-2K\tau}) \tag{346}$$

It follows that

$$(X_3)_{max} = X_0 + X_0(e^{-K\tau} + e^{-2K\tau}) = X_0(1 + e^{-K\tau} + e^{-2K\tau}) \tag{347}$$

and

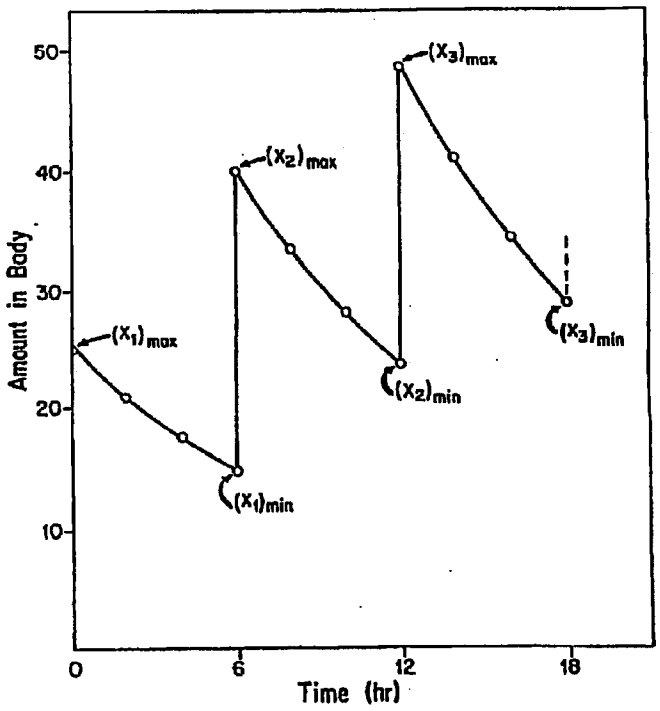

FIG. 3-1. A plot of the amount of drug in the body as a function of time following the intravenous administration (at equal time intervals) of three equal doses of a drug that confers one-compartment model characteristics on the body.

$$(X_3)_{min} = X_0(1 + e^{-K\tau} + e^{-2K\tau})e^{-K\tau} = X_0(e^{-K\tau} + e^{-2K\tau} + e^{-3K\tau}) \tag{348}$$

where $(X_3)_{max}$ is the maximum amount of drug in the body following a third dose and $(X_3)_{min}$ is the minimum amount of drug in the body τ time units after the third dose.

On examination of (341), (344), and (347) it is readily apparent that a geometric series can be written for the maximum amount of drug in the body following n doses, $(X_n)_{max}$, that is

$$(X_n)_{max} = X_0(1 + e^{-K\tau} + e^{-2K\tau} + \cdots + e^{-(n-1)K\tau}) \tag{349}$$

If we let

$$r = 1 + e^{-K\tau} + e^{-2K\tau} + \cdots + e^{-(n-1)K\tau} \tag{350}$$

it follows that

$$(X_n)_{max} = X_0 r \tag{351}$$

Multiplication of (350) by $e^{-K\tau}$ yields

$$re^{-K\tau} = e^{-K\tau} + e^{-2K\tau} + \cdots + e^{-(n-1)K\tau} + e^{-nK\tau} \tag{352}$$

which when subtracted from (350) produces

$$r - re^{-K\tau} = 1 - e^{-nK\tau} \tag{353}$$

which can be solved for r to yield

$$r = \frac{1 - e^{-nK\tau}}{1 - e^{-K\tau}} \tag{354}$$

Substitution of this value of r in (351) yields the following general expression for the maximum amount of drug in the body after intravenous administration of any number of doses:

$$(X_n)_{max} = X_0\left(\frac{1 - e^{-nK\tau}}{1 - e^{-K\tau}}\right) \tag{355}$$

From a comparison of previous equations [that is, Eqs. (341) and (343), (344) and (345), and (347) and (348)] it is equally clear that

$$(X_n)_{min} = (X_n)_{max} e^{-K\tau} \tag{356}$$

and, therefore,

$$(X_n)_{min} = X_0\left(\frac{1 - e^{-nK\tau}}{1 - e^{-K\tau}}\right)e^{-K\tau} \tag{357}$$

It is evident on examination of (355) and (357) that the amount of drug in the body at any time during a dosage interval (that is, X_n) is given by

$$X_n = X_0\left(\frac{1 - e^{-nK\tau}}{1 - e^{-K\tau}}\right)e^{-Kt} \tag{358}$$

where t is the time elapsed since dose n was administered. Equation (358) may also be written in concentration terms since $X = V \cdot C$ [according to Eq. (9)], that is

$$C_n = \frac{X_0}{V}\left(\frac{1 - e^{-nK\tau}}{1 - e^{-K\tau}}\right)e^{-Kt} \tag{359}$$

where C_n is the plasma concentration of drug during a dosing interval and V is the apparent volume of distribution of the drug. Therefore, by knowing the apparent volume of distribution and the elimination rate constant of a drug (both of which can be obtained following a single intravenous dose), the plasma concentration of a drug at any time during a dosing interval can be predicted provided a fixed dose is administered every τ time units.

Equations (358) and (359) may also be obtained by a method that does not rely on a detailed derivation of the type presented above, and consequently is significantly more convenient (see Appendix 2). Any equation which describes the time course of a drug in a driving force compartment after a single dose may be directly converted to a multiple-dose equation by multiplying each exponential term containing t by the function

$$\frac{1 - e^{-nk_1\tau}}{1 - e^{-k_1\tau}}$$

where n and τ are as defined previously and k_1 is the apparent first-order rate constant in each exponential term. Therefore, multiplication of Eq. (5), $X = X_0 e^{-Kt}$, by the multiple-dosing function, and setting k_1 equal to K [since K is the rate constant in the exponential term of (5)], Eq. (5) may be directly converted to (358), that is

$$X\left(\frac{1 - e^{-nK\tau}}{1 - e^{-K\tau}}\right) = X_0\left(\frac{1 - e^{-nK\tau}}{1 - e^{-K\tau}}\right)e^{-Kt} = X_n$$

The drug concentration in the plasma, at any given point in time during a dosing interval, will increase as the number of doses increases and approach a constant level (see Fig. 3-2). After multiple dosing for a time equal to four times the biologic half-life of a drug, the plasma concentration is within 10% of its plateau or steady-state level. After

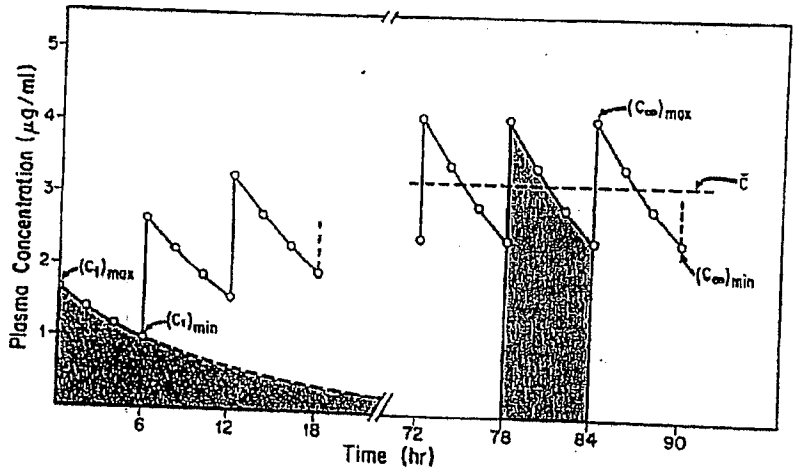

FIG. 3-2. A plot of plasma concentration versus time following the intravenous administration of equal doses of a drug, which confers one-compartment model characteristics on the body, at equal time intervals.

a period of time equal to 7 half-lives, the drug concentration, at any point in time during a dosing interval is within 1% of the plateau level. The equation describing the time course of drug at the plateau or steady-state level can be obtained by setting n in (359) to infinity (i.e., by recognizing that the term $e^{-nK\tau}$ approaches zero with increasing number of doses). Thus,

$$C_\infty = \frac{X_0}{V}\left(\frac{1}{1 - e^{-K\tau}}\right) e^{-Kt} \qquad (360)$$

where C_∞ is the plasma concentration of drug as a function of time during a dosing interval at steady state. Similarly the equations for the maximum and minimum amounts of drug in the body during a dosing interval at steady state, $(X_\infty)_{max}$ and $(X_\infty)_{min}$, respectively, can be written as

$$(X_\infty)_{max} = X_0\left(\frac{1}{1 - e^{-K\tau}}\right) \qquad (361)$$

and

$$(X_\infty)_{min} = X_0\left(\frac{1}{1 - e^{-K\tau}}\right) e^{-K\tau} \qquad (362)$$

Equations (361) and (362) can also be expressed in concentration terms, employing the relationship $X = VC$ [Eq. (9)], as follows:

$$(C_\infty)_{max} = \frac{X_0}{V}\left(\frac{1}{1 - e^{-K\tau}}\right) \qquad (363)$$

and

$$(C_\infty)_{min} = \frac{X_0}{V}\left(\frac{1}{1 - e^{-K\tau}}\right) e^{-K\tau} \qquad (364)$$

where $(C_\infty)_{max}$ and $(C_\infty)_{min}$ are the maximum and minimum plasma concentrations of drug at steady state, respectively.

A parameter which is very useful in multiple dosing is the "average" concentration of drug in the plasma at steady state, $\bar{C}$. This parameter can be defined as

$$\bar{C} = \frac{\int_0^\tau C_\infty\, dt}{\tau} \qquad (365)$$

where $\int_0^\tau C_\infty dt$ is the area under the plasma concentration-time curve at steady state during a dosing interval, i.e., between time zero and τ, where τ is as defined previously. Integration of (360) from time zero to τ yields

$$\int_0^\tau C_\infty\, dt = \frac{X_0}{VK} \qquad (366)$$

Substitution of X_0/VK for $\int_0^\tau C_\infty\, dt$ in (365) yields the following expression for $\bar{C}$:

$$\bar{C} = \frac{X_0}{VK\tau} \qquad (367)$$

Therefore, by knowing the apparent volume of distribution and elimination rate constant of a drug, both of which can be determined following a single intravenous dose, the "average" plasma concentration of a drug at steady state following the intravenous administration of a fixed

dose X_0 at a constant time interval of τ can be predicted. As can also be seen from (367), only the size of the administered dose X_0 and the time interval at which this dose is administered, τ, can be adjusted to obtain a desired "average" steady-state plasma concentration since V and K are "biological" constants for a given drug.

The "average" plasma concentration of a drug at steady state as calculated employing (365) or (367) is neither the arithmetic nor the geometric mean of $(C_\infty)_{max}$ and $(C_\infty)_{min}$. Rather, it is the plasma concentration at steady state which when multiplied by τ equals the area under the plasma concentration-time curve over the time interval zero to τ. Therefore, from simple geometric considerations, $\bar{C}$ must represent some plasma concentration between $(C_\infty)_{max}$ and $(C_\infty)_{min}$ (see Fig. 3-2). A limitation of the $\bar{C}$ approach is that it gives no information about the fluctuations in plasma levels [that is, $\bar{C}$ gives no information as to the relative magnitudes of $(C_\infty)_{max}$ and $(C_\infty)_{min}$].

It should be noted that integration of Eq. (5), $X = X_0 e^{-Kt}$, which describes the time course of the amount of drug in the body following the administration of a single intravenous dose, from time zero to infinity gives

$$\int_0^\infty X\,dt = \frac{X_0}{K} \tag{368}$$

which when converted to concentration terms [that is, $X = VC$, Eq. (9)] yields

$$\int_0^\infty C\,dt = \frac{X_0}{VK} \tag{369}$$

This expression for the area under the plasma concentration-time curve from time zero to infinity following a single intravenous dose is equivalent to (368), the equation for the area under the plasma concentration-time curve from time zero to τ during a dosing interval at steady state. Hence, the area under the plasma concentration-time curve during a dosing interval at steady state is equivalent to the total area under the curve following a single dose (Fig. 3-2). Therefore, the "average" plasma concentration of drug at steady state can be predicted from a single-dose study by employing

$$\bar{C} = \frac{\int_0^\infty C\,dt}{\tau} \tag{370}$$

which does not require the calculation of the apparent volume of distribution and elimination rate constant. This equation does assume, however, that V and K are constant over the entire dosing period.

As discussed previously, the administration of a drug on a multiple-dose regimen will result in the accumulation of drug in the body. The extent of accumulation of a given drug may be quantified in several ways. During any dosing interval the "average" plasma concentration of a drug $\bar{C}_n$ may be defined as

$$\bar{C}_n = \frac{\int_0^\tau C_n\,dt}{\tau} \tag{371}$$

where $\int_0^\tau C_n\,dt$ is the area under the plasma concentration-time curve during the nth dosing interval. Integration of (359) from time zero to τ yields

$$\int_0^\tau C_n\,dt = \frac{X_0}{VK}(1 - e^{-nK\tau}) \tag{372}$$

and therefore,

$$\bar{C}_n = \frac{X_0}{VK\tau}(1 - e^{-nK\tau}) \tag{373}$$

Substitution of $\bar{C}$ for $X_0/VK\tau$, according to (367), in (373) and rearrangement yields

$$\frac{\bar{C}_n}{\bar{C}} = 1 - e^{-nK\tau} \tag{374}$$

When n = 1, that is, for the first dose, (374) becomes

$$\frac{\bar{C}_1}{\bar{C}} = 1 - e^{-K\tau} \tag{375}$$

The inverse ratio $\bar{C}/\bar{C}_1$ may be defined as an accumulation factor R, and therefore,

$$R = \frac{1}{1 - e^{-K\tau}} \tag{376}$$

By knowing the elimination rate constant, the extent to which a drug would accumulate in the body following a fixed dosing regimen can be calculated employing (376).

Other ratios may also be used to determine the extent of drug accumulation. Conversion of (343) and (341) to concentration terms [that is, using Eq. (9)] yields

$$(C_1)_{min} = \frac{X_0}{V} e^{-K\tau} \tag{377}$$

and

$$(C_1)_{max} = \frac{X_0}{V} \tag{378}$$

respectively. The ratios $(C_\infty)_{min}$ [Eq. (364)] to $(C_1)_{min}$ [Eq. (377)] and $(C_\infty)_{max}$ [Eq. (363)] to $(C_1)_{max}$ [Eq. (378)] all equal R, that is,

$$\frac{(C_\infty)_{min}}{(C_1)_{min}} = \frac{(C_\infty)_{max}}{(C_1)_{max}} = \frac{1}{1 - e^{-K\tau}} = R \tag{379}$$

Therefore, a comparison of minimum, maximum, and "average" plasma levels of drug following the first dose and at steady state enables one to gain insight into the extent to which a drug would be expected to accumulate on multiple dosing. Consider a drug with a half-life of 24 hr (that is, $K = 0.029\ hr^{-1}$, since $K = 0.693/t_{\frac{1}{2}}$). If this drug is administered every 24 hr (that is, $\tau = 24$ hr), R equals 2.0. However, administration every 6 hr results in greater than threefold increase in the extent of accumulation since R now equals 6.3.

Equation (367) can be rearranged to yield

$$\bar{C}V = \frac{X_0}{K\tau} \tag{380}$$

where $\bar{C}V$ equals the "average" amount of drug in the body at steady state ($\bar{X}$). Thus

$$\bar{X} = \frac{X_0}{K\tau} \tag{381}$$

Dividing both sides of (381) by X_0, the intravenous dose, substituting $0.693/t_{\frac{1}{2}}$ for K [according to Eq. (12)], and rearranging, results in the expression

$$\frac{\bar{X}}{X_0} = \frac{1.44t_{\frac{1}{2}}}{\tau} \tag{382}$$

which also enables an estimate of the extent of accumulation. When τ equals the half-life of a drug, the extent of accumulation is relatively modest. If the ratio $t_{\frac{1}{2}}/\tau$ is large, however, the extent of accumulation will become significant. For example, if τ is decreased from 24 to 6 hr for a drug with a 24-hr half-life, the "average" amount of drug in the body at steady state will be almost six times as large as a single dose.

Equation (374), in addition to its utility in determining the extent of accumulation, may also be employed to calculate the time required to reach a certain fraction of the ultimate steady-state level, where the fraction of the steady-state level, f_{ss}, is defined in terms of "average" plasma levels, that is,

$$f_{ss} = \frac{\bar{C}_n}{\bar{C}} \tag{383}$$

Substitution of f_{ss} for $\bar{C}_n/\bar{C}$ in (374) yields

$$f_{ss} = 1 - e^{-nK\tau} \tag{384}$$

Therefore, for a given half-life (that is, $t_{\frac{1}{2}} = 0.693/K$) and dosing interval the fraction of the ultimate steady-state level that is reached following the nth dose can be calculated. Rearrangement of (384) yields

$$e^{-nK\tau} = 1 - f_{ss} \tag{385}$$

the common logarithm of which is

$$-nK\tau = 2.303 \log (1 - f_{ss}) \tag{386}$$

Equation (386) can be further rearranged to obtain an expression for the time required to reach a certain fraction of the steady-state level, which is given by the product of the number of doses administered and the dosing interval. Thus,

$$n\tau = -\frac{2.303}{K} \log (1 - f_{ss}) \tag{387}$$

or

$$n\tau = -3.32t_{\frac{1}{2}} \log (1 - f_{ss}) \tag{388}$$

since K equals $0.693/t_{\frac{1}{2}}$ [Eq. (12)]. Therefore, the time required to reach a particular fraction of steady state (that is, $n\tau$) is independent of the number of doses administered and the interval between administration, but it is directly proportional to the half-life of a drug. From (388) it can be readily calculated that 3.32 and 6.64 half-lives would be required to reach 90 and 99%, respectively, of the steady-state plasma level of a drug.

As (388) indicates, a significant period of time may be required to attain steady-state plasma levels for drugs with long half-lives. A rational method to overcome the lapse in time before a steady-state level is reached would be to administer an initial "loading" dose. One approach to the calculation of a "loading" dose is as follows. It is often desirable to maintain plasma concentrations of drug greater than some minimum effective level. This level may be defined as $(C_\infty)_{min}$. Therefore, the first dose (i.e., the "loading" dose, X_0^*) must be sufficiently high such that $(C_1)_{min}$ equals $(C_\infty)_{min}$, where $(C_1)_{min}$ and $(C_\infty)_{min}$ are given by (377) and (364), respectively. Substitution of X_0^* for X_0 (the maintenance dose) in (377) yields

$$(C_1)_{min} = \frac{X_0^*}{V} e^{-K\tau} \tag{389}$$

Since $(C_1)_{min}$ as given by (389) must equal $(C_\infty)_{min}$,

$$\frac{X_0^*}{V} e^{-K\tau} = \frac{X_0}{V}\left(\frac{1}{1 - e^{-K\tau}}\right) e^{-K\tau} \tag{390}$$

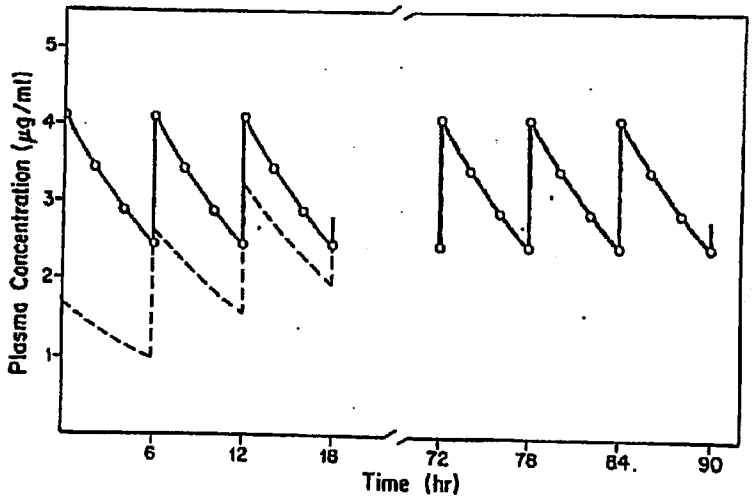

FIG. 3-3. A plot of plasma concentration versus time following repetitive intravenous administration of a drug which confers on the body the characteristics of a one-compartment model. The figure demonstrates the plasma levels resulting from the administration of either a series of maintenance doses (--) or an initial loading dose followed by a series of maintenance doses (o).

A-344

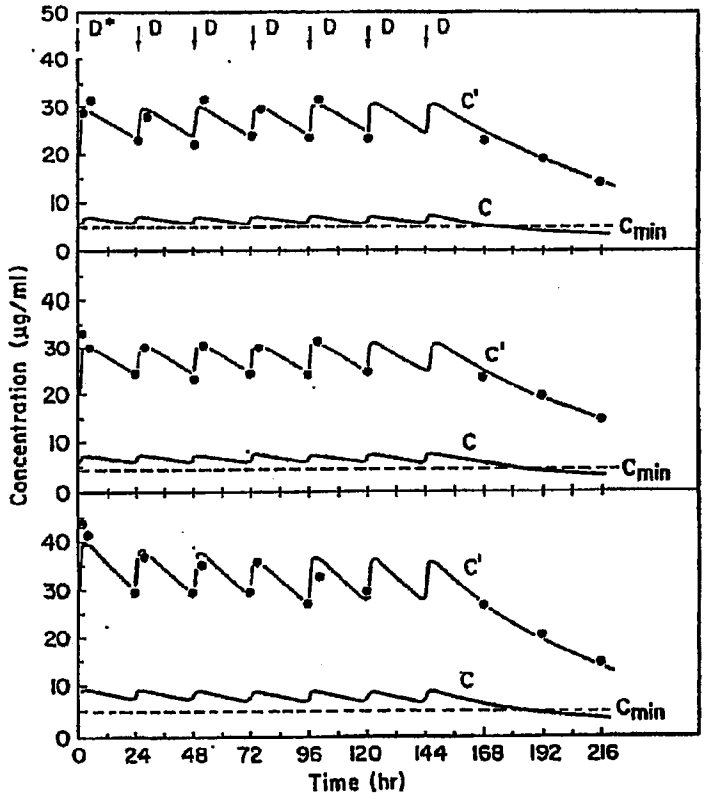

FIG. 3-4. Plasma concentrations (•) of 2-sulfa-3-methoxypyrazine in three normal adults during repetitive dosing. Loading dose $D^* = 400$ mg, maintenance dose $D = 100$ mg, $\tau = 24$ hr. Upper curves: c', calculated curves fitted to values found in plasma. Lower curves: c, calculated concentrations of unbound drug in plasma water. (From Ref. 1.)

By cancelling common terms the following expression for the determination of a "loading" dose is obtained:

$$X_0^* = X_0\left(\frac{1}{1 - e^{-K\tau}}\right) \tag{391}$$

Therefore, administration of a "loading" dose X_0^* as calculated by (391) followed by a maintenance dose X_0 every τ time units, should produce an immediate steady-state plasma level of drug (Figs. 3-3 and 3-4).

The same procedure may be employed to calculate a "loading" dose based on the "average" plasma concentrations of drug. If this approach is used, an equation for the "loading" dose identical to (391) will be obtained. To illustrate this approach, let us consider a drug with a half-life of 24 hr which is administered every 24 hr. In this case, the "loading" dose X_0^* required to achieve immediate steady-state levels will be twice the size of the maintenance dose X_0.

B. First-order Absorption

The vast majority of drugs administered on a continuous basis are administered orally. Of these, a significant fraction yield plasma drug concentration-time curves which can be described by a one-compartment model with first-order input and output. The equation describing the plasma concentration versus time curve following multiple dosing of a drug which is absorbed by an apparent first-order process can be arrived at directly. Multiplication of each exponential term in Eq. (92), which describes the time course of drug in the plasma following first-order input, by the multiple-dosing function and setting k_i in each function equal to the rate constant in each exponential term (see Appendix 2) yields

$$C_n = \frac{k_a F X_0}{V(k_a - K)}\left[\left(\frac{1 - e^{-nK\tau}}{1 - e^{-K\tau}}\right)e^{-Kt} - \left(\frac{1 - e^{-nk_a\tau}}{1 - e^{-k_a\tau}}\right)e^{-k_a t}\right] \qquad (392)$$

where C_n, V, K, n, and τ are as defined previously and t is any time from 0 to τ during a dosing interval. The constant k_a is the apparent first-order absorption rate constant and F is the fraction of the administered dose X_0 which is absorbed. Equation (392) can be employed to predict the plasma concentration of drug at any time during any dosing interval. However, information that is often difficult to obtain, such as estimates of F, V, and k_a, is required for such predictions.

At steady state the time course of drug in the plasma can be described by the equation

$$C_\infty = \frac{k_a F X_0}{V(k_a - K)}\left[\left(\frac{1}{1 - e^{-K\tau}}\right)e^{-Kt} - \left(\frac{1}{1 - e^{-k_a\tau}}\right)e^{-k_a t}\right] \qquad (393)$$

which is obtained by setting n equal to a sufficiently large number in (392) and realizing that the terms $e^{-nK\tau}$ and $e^{-nk_a\tau}$ then approach zero.

The "average" plasma concentration of drug at steady-state $\bar{C}$, as defined by (365), can also be calculated either by employing (365) directly or by employing an equation analogous to (367) which can be derived as follows. Integration of (393) from time zero to τ yields

$$\int_0^\tau C_\infty\,dt = \frac{FX_0}{VK} \qquad (394)$$

where $\int_0^\tau C_\infty\,dt$ is the area under the plasma concentration-time curve during a dosing interval at steady state. Substitution of FX_0/VK for $\int_0^\tau C\,dt$ in (365) yields the following equation for the "average" plasma concentration of drug at steady state following first-order input:

$$\bar{C} = \frac{FX_0}{VK\tau} \qquad (395)$$

As is evident from (395), $\bar{C}$ is dependent on the size of dose administered, the extent to which it is absorbed, and the dosing interval. The same "average" plasma concentration of drug will be obtained whether or not the dose X_0 is administered as a single dose every τ time units, or is subdivided and administered at different times within τ time units; that is, 600 mg once a day is equivalent to 300 mg every 12 hr, is equivalent to 150 mg every 6 hr, etc. (see Figs. 3-5 and 3-6). However, upon subdividing the dose, the difference between the minimum and maximum plasma concentration will usually decrease.

The area under the plasma concentration-time curve from time zero to infinity ($\int_0^\infty C\,dt$) following first-order input of a single dose equals FX_0/VK [Eq. (98)], which is in turn equal to the area under the plasma concentration-time curve during a dosing interval at steady state [that is, $FX_0/VK = \int_0^\tau C_\infty\,dt$, Eq. (394)]. Therefore, substitution of $\int_0^\infty C\,dt$ for $\int_0^\tau C_\infty\,dt$ in (365) yields

$$\bar{C} = \frac{\int_0^\infty C\,dt}{\tau} \qquad (370)$$

This relationship is probably more useful than (395) for predicting $\bar{C}$ since the area under the plasma concentration-time curve following a single dose is generally easily determined. Estimates of F and V which are necessary for the utilization of (395) are frequently difficult to evaluate since intravenous data is usually required.

Assuming that the fraction F of each dose absorbed is constant during a multiple-dosing regimen, the time at which a maximum plasma concentration of drug at steady state occurs (t_0') may be arrived at by differentiating (393) with respect to time and setting the resultant equal to zero. Thus

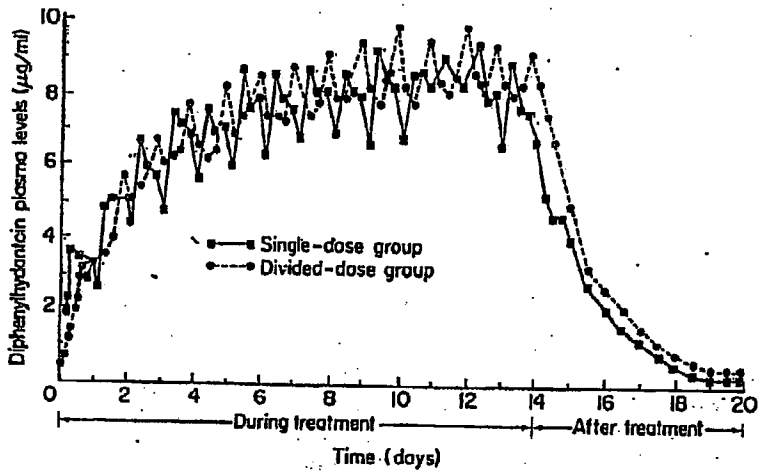

FIG. 3-5. Mean plasma levels of diphenylhydantoin (DPH) following oral administration of 100 mg DPH three times a day (divided-dose group) or 300 mg DPH once a day (single-dose group). Each group consisted of 12 normal adult volunteers. (From Ref. 2.)

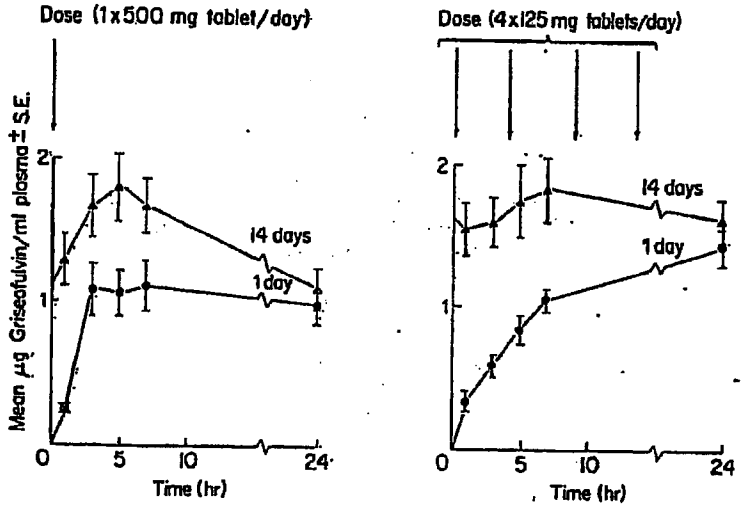

FIG. 3-6. Average plasma concentrations of griseofulvin in 10 human volunteers after 1 and 14 days of oral treatment. (From Ref. 3.)

$$\frac{dC_{ss}}{dt} = \frac{k_a F X_0}{V(k_a - K)}\left(\frac{k_a e^{-k_a t'_p}}{1 - e^{-k_a \tau}} - \frac{K e^{-K t'_p}}{1 - e^{-K\tau}}\right) = 0 \qquad (396)$$

and

$$\frac{k_a e^{-k_a t'_p}}{1 - e^{-k_a \tau}} = \frac{K e^{-K t'_p}}{1 - e^{-K\tau}} \qquad (397)$$

Rearrangement of (397) yields

$$e^{(k_a - K)t'_p} = \frac{k_a(1 - e^{-K\tau})}{K(1 - e^{-k_a \tau})} \qquad (398)$$

By taking the common logarithm of both sides of (398) and dividing by $k_a - K$, the following expression for the time at which the maximum plasma concentration at steady state occurs is obtained:

$$t'_p = 2.303 \log \frac{k_a(1 - e^{-K\tau})/K(1 - e^{-k_a \tau})}{k_a - K} \qquad (399)$$

The time t_p at which a maximum plasma concentration occurs following a single dose is given by

$$t_p = 2.303 \log \frac{k_a/K}{k_a - K} \qquad (104)$$

Subtraction of (399) from (104) yields

$$t_p - t'_p = 2.303 \log \frac{(1 - e^{-k_a \tau})/(1 - e^{-K\tau})}{k_a - K} \qquad (400)$$

Since the right side of this equation is always positive, it is apparent that the maximum plasma concentration occurs at an earlier time at steady state than following a single dose. Frequently, the time at which the maximum plasma concentration is observed after the first dose t_p is the time at which the plasma is sampled after administration of subsequent doses. Based on mathematical principles this would not be a sound practice since the time at which a maximum plasma concentration

occurs is not constant until steady state is achieved. Moreover, biological variability would add to the undesirability of such an approach.

Once t'_p is known, the maximum plasma concentration at steady-state $(C_\infty)_{max}$ can be derived. Substitution of t'_p for time in (393) yields

$$(C_\infty)_{max} = \frac{k_a F X_0}{V(k_a - K)}\left[\left(\frac{1}{1-e^{-K\tau}}\right)e^{-Kt'_p} - \left(\frac{1}{1-e^{-k_a\tau}}\right)e^{-k_a t'_p}\right] \quad (401)$$

By rearrangement of (397) the following expression for the term $e^{-k_a t'_p}$ can be obtained:

$$e^{-k_a t'_p} = \left(\frac{1-e^{-k_a\tau}}{1-e^{-K\tau}}\right)\frac{K}{k_a}e^{-Kt'_p} \quad (402)$$

Substituting this value of $e^{-k_a t'_p}$ into (401) yields

$$(C_\infty)_{max} = \frac{k_a F X_0}{V(k_a - K)}\left[\left(\frac{1}{1-e^{-K\tau}}\right)e^{-Kt'_p} - \left(\frac{1}{1-e^{-k_a\tau}}\right)\left(\frac{1-e^{-k_a\tau}}{1-e^{-K\tau}}\right)\frac{K}{k_a}e^{-Kt'_p}\right] \quad (403)$$

which can be simplified to

$$(C_\infty)_{max} = \frac{FX_0}{V}\left(\frac{1}{1-e^{-K\tau}}\right)e^{-Kt'_p} \quad (404)$$

Following the first dose the maximum plasma concentration $(C_1)_{max}$ is given by

$$(C_1)_{max} = \frac{FX_0}{V}e^{-Kt_p} \quad (108)$$

Therefore, an accumulation factor R can be calculated since $R = (C_\infty)_{max}/(C_1)_{max}$ [Eq. (379)]. Thus,

$$R = \frac{1}{1-e^{-K\tau}}\frac{e^{-Kt'_p}}{e^{-Kt_p}} \quad (405)$$

This is a relatively complicated relationship for the determination of accumulation since t_p and t'_p are complex functions of the absorption

and elimination rate constants, and consequently utilization of maximum plasma concentration values to quantify accumulation is not very attractive.

A simpler approach would be to compare the minimum plasma concentrations of drug at steady state and following the first dose to evaluate accumulation, that is, $R = (C_\infty)_{min}/(C_1)_{min}$ [Eq. (379)]. However, this method is relatively simple only when one is dealing with a situation in which each dose is administered in the postabsorptive phase of the preceding dose. This situation probably exists for a large number of drugs although it may not be valid for sustained release products and for drugs which are very slowly absorbed.

By setting n equal to one and t equal to τ in (392), an expression for the minimum plasma concentration following the first dose $(C_1)_{min}$ can be obtained, that is,

$$(C_1)_{min} = \frac{k_a F X_0}{V(k_a - K)}(e^{-K\tau} - e^{-k_a\tau}) \quad (406)$$

Similarly, by setting t equal to τ in (393), the following expression for the minimum plasma concentration at steady state $(C_\infty)_{min}$ results:

$$(C_\infty)_{min} = \frac{k_a F X_0}{V(k_a - K)}\left[\left(\frac{1}{1-e^{-K\tau}}\right)e^{-K\tau} - \left(\frac{1}{1-e^{-k_a\tau}}\right)e^{-k_a\tau}\right] \quad (407)$$

In the postabsorptive phase (that is, as $e^{-k_a\tau}$ approaches zero), (406) and (407) become

$$(C_1)_{min} = \frac{k_a F X_0}{V(k_a - K)}e^{-K\tau} \quad (408)$$

and

$$(C_\infty)_{min} = \frac{k_a F X_0}{V(k_a - K)}\left(\frac{1}{1-e^{-K\tau}}\right)e^{-K\tau} \quad (409)$$

respectively. Therefore, the accumulation factor $(C_\infty)_{min}/(C_1)_{min}$ is $R = 1/(1-e^{-K\tau})$ [Eq. (376)]. This expression can be readily employed to determine the extent of accumulation following first-order input every τ time units since only an estimate of the elimination rate constant is required.

As discussed previously, following intravenous administration of a drug, the ratio $\bar{X}/X_0$ can also be used to estimate the extent to which

accumulation will occur following first-order input. Rearranging (395) and setting the product $\bar{C}V$ equal to $\bar{X}$, the average amount of drug in the body at steady state, yields

$$\bar{X} = \frac{FX_0}{K\tau} \tag{410}$$

Substitution of $0.693/t_{\frac{1}{2}}$ for K [Eq. (12)] and rearrangement gives

$$\frac{\bar{X}}{FX_0} = \frac{1.44t_{\frac{1}{2}}}{\tau} \tag{411}$$

where the extent of accumulation, as measured by comparing the "average" steady-state body level to the amount absorbed from the maintenance dose, is directly proportional to the ratio of the biologic half-life and dosing interval.

The time required to reach a certain fraction of the ultimate steady state following first-order input can also be estimated, where the fraction of the steady-state level (f_{ss}) is as defined by Eq. (383), that is, $f_{ss} = \bar{C}_n/\bar{C}$, where $\bar{C}_n = \int_0^\tau C_n\,dt/\tau$ [Eq. (371)] and $\bar{C} = FX_0/VK\tau$ [Eq. (395)]. Integration of (392) from time zero to τ yields

$$\int_0^\tau C_n\,dt = \frac{k_a FX_0}{V(k_a - K)}\left[\left(\frac{1 - e^{-nk_a\tau}}{1 - e^{-k_a\tau}}\right)\frac{e^{-k_a\tau}}{k_a} - \left(\frac{1 - e^{-nK\tau}}{1 - e^{-K\tau}}\right)\frac{e^{-K\tau}}{K} + \left(\frac{1 - e^{-nK\tau}}{1 - e^{-K\tau}}\right)\frac{1}{K} - \left(\frac{1 - e^{-nk_a\tau}}{1 - e^{-k_a\tau}}\right)\frac{1}{k_a}\right] \tag{412}$$

which on rearrangement and simplification becomes

$$\int_0^\tau C_n\,dt = \frac{FX_0}{VK}\left(1 + \frac{Ke^{-nk_a\tau}}{k_a - K} - \frac{k_a e^{-nK\tau}}{k_a - K}\right) \tag{413}$$

Substitution of the value of $\int_0^\tau C_n\,dt$, as given in (413), into (371) yields the following expression for the "average" plasma concentration of drug during the nth dosing interval:

$$\bar{C}_n = \frac{FX_0}{VK\tau}\left(1 + \frac{Ke^{-nk_a\tau}}{k_a - K} - \frac{k_a e^{-nK\tau}}{k_a - K}\right) \tag{414}$$

By substituting $\bar{C}$ for $FX_0/VK\tau$ according to (395) in (414), and dividing both sides of the equation by $\bar{C}$, one obtains

$$f_{ss} = \frac{\bar{C}_n}{\bar{C}} = \left(1 + \frac{Ke^{-nk_a\tau}}{k_a - K} - \frac{k_a e^{-nK\tau}}{k_a - K}\right) \tag{415}$$

From (415) it is readily apparent that the time required to reach a certain fraction of the steady-state level is a complex function of the absorption and elimination rate constants. The larger the value of k_a relative to K, the less dependent on k_a is the time required to reach a given fraction of steady state. At very large values of k_a relative to K (that is, $k_a/K \geq 10$) Eq. (415) approaches

$$f_{ss} = 1 - e^{-nK\tau} \tag{384}$$

Therefore,

$$n\tau = -3.32t_{\frac{1}{2}} \log (1 - f_{ss}) \tag{388}$$

which is readily arrived at from Eq. (385) [4]. Hence, when the absorption rate constant is significantly larger than the elimination rate constant, the time required ($n\tau$) to reach a certain fraction of the steady-state level is a function only of drug elimination [that is, K or $t_{\frac{1}{2}}$, where $t_{\frac{1}{2}} = 0.693/K$, Eq. (12)]. If this is not the case, then f_{ss} is dependent on k_a. The smaller the value of k_a, the longer the time required to attain steady state or some fraction thereof.

As discussed in the section on multiple dosing by intravenous administration, an initial "loading" dose may be desirable, since for drugs with long half-lives a long period of time is required to reach steady state. The "loading" dose X_0^* required to achieve steady-state levels on the first dose may be determined by letting X_0 equal X_0^* in Eq. (406) [the equation for $(C_1)_{min}$] and setting this equal to the equation for $(C_\infty)_{min}$ [Eq. (407)], that is,

$$\frac{k_a FX_0^*}{V(k_a - K)}\left(e^{-K\tau} - e^{-k_a\tau}\right) = \frac{k_a FX_0}{V(k_a - K)}\left(\frac{e^{-K\tau}}{1 - e^{-K\tau}} - \frac{e^{-k_a\tau}}{1 - e^{-k_a\tau}}\right) \tag{416}$$

By cancelling common terms, bringing the right side of the equation to a common denominator, and dividing by $e^{-K\tau} - e^{-k_a\tau}$, one obtains

$$X_0^* = X_0\left[\frac{e^{-K\tau} - e^{-K\tau}e^{-k_a\tau} - e^{-k_a\tau} + e^{-K\tau}e^{-k_a\tau}}{(1 - e^{-K\tau})(1 - e^{-k_a\tau})(e^{-K\tau} - e^{-k_a\tau})}\right] \tag{417}$$

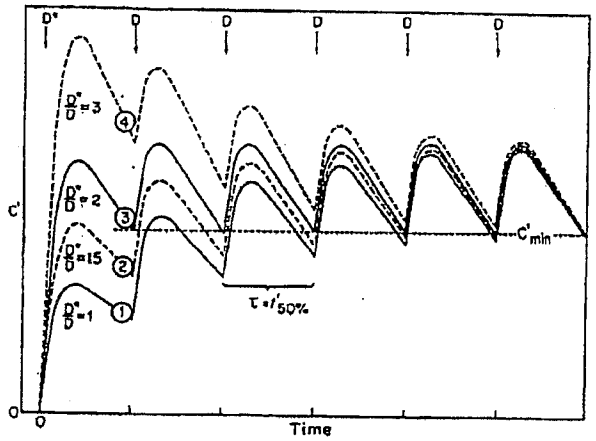

FIG. 3-7. Concentration (c') curves of a drug in the plasma for dosage schedules with equal maintenance doses D and dosing intervals (τ, set equal to the half-life of the drug, $t'_{50\%}$) but different loading doses D^*, such that D^*/D varies from 1 to 3. (From Ref. 5.)

Further simplification gives

$$X_0^* = X_0\left[\frac{1}{(1 - e^{-K\tau})(1 - e^{-k_a\tau})}\right] \qquad (418)$$

If the maintenance dose is administered in the postabsorptive phase of the loading dose, (418) can be further simplified since the term $e^{-K_a\tau}$ approaches zero and

$$X_0^* = X_0\left(\frac{1}{1 - e^{-K\tau}}\right) \qquad (391)$$

which was the equation employed to calculate a loading dose for drugs administered by the intravenous route. Irrespective of the size of the initial dose the steady-state plasma concentration of drug ultimately reached will be the same since the steady-state level is governed by the size of the maintenance dose (Fig. 3-7).

II. TWO-COMPARTMENT MODEL

A. Intravenous Injection

Plasma levels of a drug which after intravenous administration confers upon the body the characteristics of a two-compartment model can be described by

$$C = \frac{X_0(\alpha - k_{21})}{V_c(\alpha - \beta)}e^{-\alpha t} + \frac{X_0(k_{21} - \beta)}{V_c(\alpha - \beta)}e^{-\beta t} \qquad (153)$$

where α and β are the fast and slow disposition rate constants, respectively, and k_{21} is an intercompartmental transfer rate constant. V_c is the apparent volume of the central compartment. See Chap. 2 for a more detailed discussion of these parameters. The plasma concentration at any time during a dosing interval can be determined directly by multiplying each exponential term in (153) by the multiple-dosing function (see Appendix 2) and setting k_1 in each function equal to the disposition rate constant in each exponential term, that is

$$C_n = \frac{X_0(\alpha - k_{21})}{V_c(\alpha - \beta)}\left(\frac{1 - e^{-n\alpha\tau}}{1 - e^{-\alpha\tau}}\right)e^{-\alpha t} + \frac{X_0(k_{21} - \beta)}{V_c(\alpha - \beta)}\left(\frac{1 - e^{-n\beta\tau}}{1 - e^{-\beta\tau}}\right)e^{-\beta t} \qquad (419)$$

where t is any time during a dosing interval of length τ time units (that is, $0 \le t \le \tau$) and n is the number of doses administered. At steady state the terms $e^{-n\alpha\tau}$ and $e^{-n\beta\tau}$ approach zero, and therefore (419) reduces to

$$C_\infty = \frac{X_0(\alpha - k_{21})}{V_c(\alpha - \beta)}\left(\frac{1}{1 - e^{-\alpha\tau}}\right)e^{-\alpha t} + \frac{X_0(k_{21} - \beta)}{V_c(\alpha - \beta)}\left(\frac{1}{1 - e^{-\beta\tau}}\right)e^{-\beta t} \qquad (420)$$

where C_∞ is the plasma concentration of drug at any time during a dosage interval at steady state following intravenous administration. Equation (420) can also be written in the form

$$C_\infty = Ue^{-\alpha t} + We^{-\beta t} \qquad (421)$$

where

$$U = \frac{X_0(\alpha - k_{21})}{V_c(\alpha - \beta)}\left(\frac{1}{1 - e^{-\alpha\tau}}\right) \qquad (422)$$

and

$$W = \frac{X_0(k_{21} - \beta)}{V_C(\alpha - \beta)}\left(\frac{1}{1 - e^{-\beta\tau}}\right) \tag{423}$$

Therefore, from a semilogarithmic plot of plasma concentration versus time during a dosage interval at steady state, U, W, α, and β can be estimated (see method of residuals, Appendix 3). For such estimates to be made, however, τ must be sufficiently large such that administration occurs in the postdistributive phase of the preceding dose. Substitution of A for $X_0(\alpha - k_{21})/V_C(\alpha - \beta)$ and B for $X_0(k_{21} - \beta)/V_C(\alpha - \beta)$, according to (155) and (156), respectively, in (422) and (423) yields

$$U = A\left(\frac{1}{1 - e^{-\alpha\tau}}\right) \tag{424}$$

and

$$W = B\left(\frac{1}{1 - e^{-\beta\tau}}\right) \tag{425}$$

where A and B are the zero-time intercepts following a single intravenous dose. Solving (424) and (425) for A and B, respectively, yields the following expressions:

$$A = U(1 - e^{-\alpha\tau}) \tag{426}$$

and

$$B = W(1 - e^{-\beta\tau}) \tag{427}$$

Therefore, after U, W, α, and β have been determined, A and B can be calculated, and by knowing A, B, α, and β, the parameters for a two-compartment model V_C, k_{21}, k_{10}, k_{12}, and V_B can be calculated employing (163), (165), (166), (167), and (237), respectively.

As discussed in Chap. 2, one frequently finds that the larger the ratio of the zero-time intercepts A/B, the more readily one can discern the two-compartment characteristics of a drug. Following the administration of a single intravenous dose the ratio of A to B is given by

$$\frac{A}{B} = \frac{\alpha - k_{21}}{k_{21} - \beta} \tag{270}$$

However, when a drug is continually administered until attainment of steady state the analogous ratio U/W is

$$\frac{U}{W} = \frac{A(1 - e^{-\beta\tau})}{B(1 - e^{-\alpha\tau})} \tag{428}$$

where U and W are as given by (424) and (425), respectively. Therefore, the ratio U/W will always be less than the ratio A/B since α is by definition greater than β, and hence the ratio $(1 - e^{-\beta\tau})/(1 - e^{-\alpha\tau})$ will always be less than one. Consequently, following multiple dosing the ability to discern the two-compartment characteristics of a drug is usually decreased. For a more detailed discussion of this phenomenon see page 75 in Chap. 2.

The "average" plasma concentration of a drug at steady state $\bar{C}$, as defined by Eq. (365), $\bar{C} = \int_0^\tau C_\infty\, dt/\tau$, can be derived for a drug which upon intravenous administration confers two-compartment model characteristics to the body. The area under the plasma concentration-time curve during a dosing interval at steady state can be obtained by integrating (421) from time zero to τ, that is,

$$\int_0^\tau C_\infty\, dt = \frac{U}{\alpha}(1 - e^{-\alpha\tau}) + \frac{W}{\beta}(1 - e^{-\beta\tau}) \tag{429}$$

Substitution for U and W, according to (424) and (425), respectively, in (429) yields

$$\int_0^\tau C_\infty\, dt = \frac{A}{\alpha} + \frac{B}{\beta} \tag{430}$$

which is equal to the area under the plasma concentration-time curve from time zero to infinity after a single dose, that is,

$$\int_0^\infty C\, dt = \frac{A}{\alpha} + \frac{B}{\beta} \tag{431}$$

The latter is readily obtained by integration of (154) from time zero to infinity. Also, by arranging (232), it can be shown that

$$\int_0^\infty C\, dt = \frac{X_0}{V_C k_{10}} \tag{432}$$

where V_C and k_{10} are the apparent volume of and elimination rate constant from the central compartment, respectively. Therefore,

$$\int_0^\tau C_\infty\, dt = \frac{X_0}{V_C k_{10}} \tag{433}$$

and the "average" plasma concentration of a drug at steady-state $\bar{C}$ is given by

$$\bar{C} = \frac{X_0}{V_C k_{10} \tau} \tag{434}$$

Since $V_C k_{10}$ equals $V_B \beta$ [Eq. (237)], $\bar{C}$ can also be given by

$$\bar{C} = \frac{X_0}{V_B \beta \tau} \tag{435}$$

Therefore, by knowing the apparent volume of distribution and the elimination rate constant of a drug, the "average" plasma concentration at steady state can be predicted for any intravenous dose administered every τ time units. It is also obvious from previous equations that

$$\bar{C} = \frac{\int_0^\infty C \, dt}{\tau} \tag{436}$$

and therefore the "average" plasma concentration of drug at steady state can be calculated from the area under the curve following a single dose.

The minimum concentration of drug in the plasma during a dosage interval $(C_n)_{min}$ can be determined by setting t equal to τ in (419), that is

$$(C_n)_{min} = \frac{X_0(\alpha - k_{21})}{V_C(\alpha - \beta)} \left(\frac{1 - e^{-n\alpha\tau}}{1 - e^{-\alpha\tau}}\right) e^{-\alpha\tau} + \frac{X_0(k_{21} - \beta)}{V_C(\alpha - \beta)} \left(\frac{1 - e^{-n\beta\tau}}{1 - e^{-\beta\tau}}\right) e^{-\beta\tau} \tag{437}$$

Similarly, the minimum plasma concentration at steady state $(C_\infty)_{min}$ is given by

$$(C_\infty)_{min} = \frac{X_0(\alpha - k_{21})}{V_C(\alpha - \beta)} \left(\frac{1}{1 - e^{-\alpha\tau}}\right) e^{-\alpha\tau} + \frac{X_0(k_{21} - \beta)}{V_C(\alpha - \beta)} \left(\frac{1}{1 - e^{-\beta\tau}}\right) e^{-\beta\tau} \tag{438}$$

From these two equations an accumulation factor R can be readily calculated since $R = (C_\infty)_{min}/(C_1)_{min}$ [Eq. (379)]. Therefore, by setting n equal to one in (437),

$$R = \frac{(\alpha - k_{21})\left(\frac{1}{1 - e^{-\alpha\tau}}\right) e^{-\alpha\tau} + (k_{21} - \beta)\left(\frac{1}{1 - e^{-\beta\tau}}\right) e^{-\beta\tau}}{(\alpha - k_{21})e^{-\alpha\tau} + (k_{21} - \beta)e^{-\beta\tau}} \tag{439}$$

which is a very complex relationship. However, assuming each dose is administered in the postdistributive phase of the preceding dose, the term $e^{-\alpha\tau}$ will approach zero and (439) reduces to

$$R = \frac{1}{1 - e^{-\beta\tau}} \tag{440}$$

which is identical in form to the equation for R in a one-compartment model [Eq. (376)]. Therefore, if τ is sufficiently long such that each dose is administered in the postdistributive phase of the preceding dose, the extent of accumulation can be predicted simply by knowing the elimination rate constant of a drug, β.

Administration of an initial "loading" dose, X_0^*, would enable the immediate attainment of steady-state plasma levels. This approach would be of particular importance for drugs with long half-lives for which steady-state levels are required for therapeutic effectiveness. The "loading" dose required to immediately reach steady state can be calculated by setting n equal to one and X_0 equal to X_0^* (the required loading dose) in the equation for $(C_n)_{min}$ [Eq. (437)], that is

$$(C_1)_{min} = \frac{X_0^*(\alpha - k_{21})}{V_C(\alpha - \beta)} e^{-\alpha\tau} + \frac{X_0^*(k_{21} - \beta)}{V_C(\alpha - \beta)} e^{-\beta\tau} \tag{441}$$

and then setting $(C_1)_{min}$ equal to $(C_\infty)_{min}$ [Eq. (438)]. Thus,

$$\frac{X_0^*}{V_C(\alpha - \beta)} [(\alpha - k_{21})e^{-\alpha\tau} + (k_{21} - \beta)e^{-\beta\tau}] = \frac{X_0}{V_C(\alpha - \beta)} \left[\left(\frac{\alpha - k_{21}}{1 - e^{-\alpha\tau}}\right) e^{-\alpha\tau} + \left(\frac{k_{21} - \beta}{1 - e^{-\beta\tau}}\right) e^{-\beta\tau}\right] \tag{442}$$

Solving (442) for X_0^* and cancelling common terms yields the following expression:

$$X_0^* = X_0 \left[\frac{\left(\frac{\alpha - k_{21}}{1 - e^{-\alpha\tau}}\right) e^{-\alpha\tau} + \left(\frac{k_{21} - \beta}{1 - e^{-\beta\tau}}\right) e^{-\beta\tau}}{(\alpha - k_{21})e^{-\alpha\tau} + (k_{21} - \beta)e^{-\beta\tau}}\right] \tag{443}$$

If the second dose (i.e., the maintenance dose) is administered in the postdistributive phase of the loading dose, the term $e^{-\alpha\tau}$ approaches zero and (443) can be simplified to yield

$$X_0^* = X_0 \left(\frac{1}{1 - e^{-\beta\tau}}\right) \tag{444}$$

Therefore, once the maintenance dose X_0 and dosing interval have been determined to produce the desired steady-state plasma levels of drug, the "loading" dose X_0^* can be readily estimated from (444).

B. First-order Absorption

First-order absorption of drugs which confer two-compartment characteristics to the body, yield plasma levels as a function of time which are described by equation (279). Upon multiple dosing the plasma levels of drug during any dosing interval n are given by

$$C_n = \frac{k_a F X_0}{V_c}\left[\frac{k_{21}-\alpha}{(k_a-\alpha)(\beta-\alpha)}\left(\frac{1-e^{-n\alpha\tau}}{1-e^{-\alpha\tau}}\right)e^{-\alpha t} + \frac{k_{21}-\beta}{(k_a-\beta)(\alpha-\beta)}\left(\frac{1-e^{-n\beta\tau}}{1-e^{-\beta\tau}}\right)e^{-\beta t} + \frac{k_{21}-k_a}{(\alpha-k_a)(\beta-k_a)}\left(\frac{1-e^{-nk_a\tau}}{1-e^{-k_a\tau}}\right)e^{-k_a t}\right] \quad (445)$$

where $0 \le t \le \tau$. Equation (445) is obtained by multiplying each exponential term in (279) by the multiple-dosing function (see Appendix 2) and setting k_1 in each function equal to the rate constant in each exponential term. Equation (445) can also be written

$$C_n = L\left(\frac{1-e^{-n\alpha\tau}}{1-e^{-\alpha\tau}}\right)e^{-\alpha t} + M\left(\frac{1-e^{-n\beta\tau}}{1-e^{-\beta\tau}}\right)e^{-\beta t} + N\left(\frac{1-e^{-nk_a\tau}}{1-e^{-k_a\tau}}\right)e^{-k_a t} \quad (446)$$

where L, M, and N are as defined by (282), (283), and (284), respectively.

Once steady state is attained (i.e., the terms $e^{-n\alpha\tau}$, $e^{-n\beta\tau}$, and $e^{-nk_a\tau}$ approach zero), (446) becomes

$$C_\infty = L\left(\frac{1}{1-e^{-\alpha\tau}}\right)e^{-\alpha t} + M\left(\frac{1}{1-e^{-\beta\tau}}\right)e^{-\beta t} + N\left(\frac{1}{1-e^{-k_a\tau}}\right)e^{-k_a t} \quad (447)$$

where C_∞ is the plasma concentration of drug during a dosing interval at steady state. Integration of (447) from time zero to τ yields the area under the plasma concentration versus time curve at steady state, that is,

$$\int_0^\tau C_\infty\, dt = \frac{L}{\alpha} + \frac{M}{\beta} + \frac{N}{k_a} \quad (448)$$

which is equal to $\int_0^\infty C\, dt$ following a single dose [Eq. (285)]. The area under the curve after a single dose is also given by

$$\int_0^\infty C\, dt = \frac{FX_0}{V_c k_{10}} \quad (290)$$

and therefore

$$\int_0^\tau C_\infty\, dt = \frac{FX_0}{V_c k_{10}} \quad (449)$$

where k_{10} is the elimination rate constant from the central compartment. Since $\bar{C}$ is equal to $\int_0^\tau C_\infty\, dt/\tau$ [Eq. (365)],

$$\bar{C} = \frac{FX_0}{V_c k_{10}\tau} \quad (450)$$

Furthermore, $V_c k_{10}$ equals $V_B\beta$ [Eq. (237)], and therefore $\bar{C}$ is also given as follows:

$$\bar{C} = \frac{FX_0}{V_B\beta\tau} \quad (451)$$

It follows that the "average" plasma concentration of a drug at steady state is independent of α and the absorption rate constant, and can be predicted employing (451) provided the fraction of dose absorbed, the apparent volume of distribution, and the elimination rate constant of a drug are known.

A more useful approach, which would not require estimates of F, V_B, and β, is based on the equality $\int_0^\tau C_\infty\, dt = \int_0^\infty C\, dt$ and is given as $\bar{C} = \int_0^\infty C\, dt/\tau$ [Eq. (436)]. This equation can be employed regardless of the route of administration (provided F is independent of dose number), and for any N compartment mammillary model provided elimination occurs exclusively from the central compartment. The utility of this approach for predicting $\bar{C}$ is illustrated by Fig. 3-8.

As has been discussed previously, the extent to which a drug will accumulate following multiple dosing can be determined by comparing the minimum plasma concentrations of drug at steady state with that after the first dose [i.e., the accumulation factor R equals $(C_\infty)_{min}/(C_1)_{min}$, Eq. (379)]. The equations for the minimum plasma concentrations following the first dose and any dose in the steady state can be obtained by setting t equal to τ in (446) and (447), and setting n equal to one in (446). Therefore,

$$(C_1)_{min} = Le^{-\alpha\tau} + Me^{-\beta\tau} + Ne^{-k_a\tau} \quad (452)$$

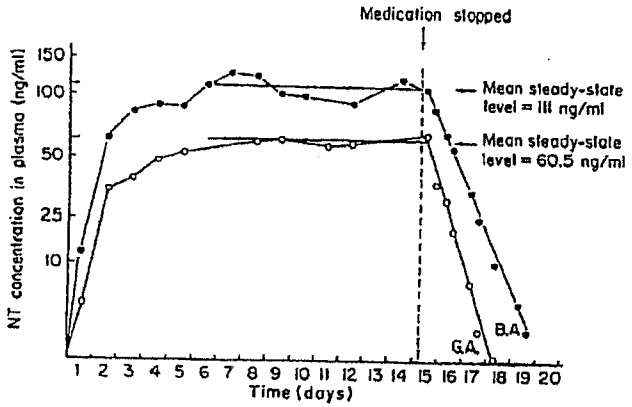

FIG. 3-8. Semilogarithmic plot of nortriptyline (NT) concentration in the plasma versus time after multiple doses (0.4 mg/kg, three times a day) to two normal subjects, G.A. (o) and B.A. (•). Mean steady-state levels predicted after single-dose administration of NT to these subjects are 53 ng/ml and 116 ng/ml for G.A. and B.A., respectively. (From Ref. 6.)

and

$$(C_\infty)_{min} = L\left(\frac{1}{1-e^{-\alpha\tau}}\right)e^{-\alpha\tau} + M\left(\frac{1}{1-e^{-\beta\tau}}\right)e^{-\beta\tau} + N\left(\frac{1}{1-e^{-k_a\tau}}\right)e^{-k_a\tau} \tag{453}$$

Hence

$$R = \frac{L\left(\frac{1}{1-e^{-\alpha\tau}}\right)e^{-\alpha\tau} + M\left(\frac{1}{1-e^{-\beta\tau}}\right)e^{-\beta\tau} + N\left(\frac{1}{1-e^{-k_a\tau}}\right)e^{-k_a\tau}}{Le^{-\alpha\tau} + Me^{-\beta\tau} + Ne^{-k_a\tau}} \tag{454}$$

However, if τ is of sufficient length such that the drug is administered in the postabsorptive, postdistributive phase of the preceding dose, then (454) simplifies to

$$R = \frac{1}{1-e^{-\beta\tau}} \tag{440}$$

This equation readily permits the estimation of the extent to which a drug accumulates in the body following first-order input. Only an estimate of the elimination rate constant is required.

The same approach for calculating a "loading" dose as used in Sec. II.A can be used for drugs administered by first-order input (i.e., by administering an initial "loading" dose X_0^* of sufficient magnitude such that $(C_1)_{min} = (C_\infty)_{min}$). The analogous expression to Eq. (443) would then be

$$X_0^* = X_0\left[\frac{\frac{k_{21}-\alpha}{(k_a-\alpha)(\beta-\alpha)}e^{-\alpha\tau} + \frac{k_{21}-\beta}{(k_a-\beta)(\alpha-\beta)}e^{-\beta\tau} + \frac{k_{21}-k_a}{(\alpha-k_a)(\beta-k_a)}e^{-k_a\tau}}{\frac{k_{21}-\alpha}{(k_a-\alpha)(\beta-\alpha)}e^{-\alpha\tau} + \frac{k_{21}-\beta}{(k_a-\beta)(\alpha-\beta)}e^{-\beta\tau} + \frac{k_{21}-k_a}{(\alpha-k_a)(\beta-k_a)}e^{-k_a\tau}}\right] \tag{455}$$

However, by administration of the maintenance dose in the postabsorptive, postdistributive phase of the "loading" dose the following equation is obtained:

$$X_0^* = X_0\frac{1}{1-e^{-\beta\tau}} \tag{444}$$

from which it is relatively simple to estimate a "loading" dose.

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Chapter 4

BIOAVAILABILITY

Bioavailability has been defined as the measurement of both the relative amount of an administered dose that reaches the general circulation (i.e., the extent of absorption of a given dose) and the rate at which this occurs [1]. For drugs that are administered on a continuous basis (i.e., in a "chronic" fashion), the total amount of drug absorbed is usually much more critical than its rate of absorption. This point has been amply demonstrated in the previous chapter. However, the absorption rate (rather than the extent of absorption) may be the more critical pharmacokinetic parameter in the totality of drug effect of those substances that may be used effectively as a single dose. A drug that enters the circulation very rapidly might induce, initially, untoward reactions if the body burden is excessive. On the other hand, if the drug is absorbed too slowly, it may not achieve sufficient body levels to produce a desired effect or a desired intensity of pharmacologic response, even if the entire dose is ultimately absorbed. It is equally obvious that the onset of pharmacologic response from a single dose of a drug is directly influenced by the rate of availability. Also, in our view, it is fair to state that the significant present-day interest in absorption kinetics has been stimulated by pharmaceutical scientists in their quest for in vitro methodology which will provide data to mirror dosage form performance with respect to drug release in and absorption from the gastrointestinal tract. We must state at the outset that assessments of the rate of availability is one of the most difficult problems encountered in developing a pharmacokinetic profile of a drug since these assessments are always model-dependent and must frequently be attempted with the most shocking paucity of data.

SCHEDULE 4

SUMMARY OF RESULTS
SECTION 1.0: DAY 7 RAW (NON-NORMALIZED) PLASMA DILTIAZEM
Mean Pharmacokinetic Parameters for Raw Plasma Diltiazem
(n=23)

Parameter	Biovail ER (A) 1 x 120 mg Arithmetic Mean (%CV)	Biovail ER(B) 1 x 240 mg Arithmetic Mean (%CV)	Biovail ER (C) 1 x 300 mg Arithmetic Mean (%CV)
AUC (0 - τ*)(ng·hr/mL)	886.61 (25.64)	2217.41 (27.80)	2799.66 (22.86)
C_{max} (ng/mL)	61.34 (29.40)	149.89 (34.26)	193.06 (27.45)
C_{min} (ng/mL)	19.50 (39.32)	51.56 (43.55)	60.65 (44.37)
T_{max} (hours)	9.96 (28.96)	10.13 (22.53)	9.61 (25.63)
Degree of Fluctuation (%)	114.74 (36.96)	108.23 (35.34)	114.55 (37.60)

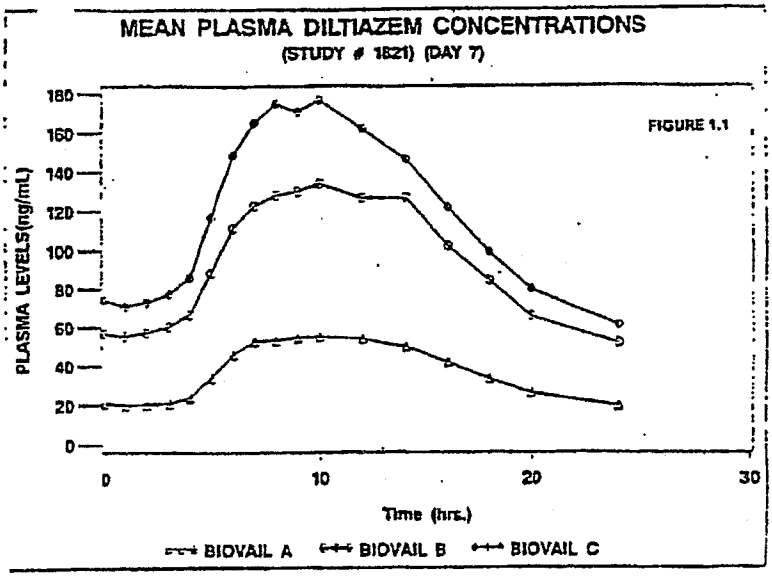
*τ = 24 hours

Linear Regression Analyses

	Intercept	Slope	r^2
AUC (0 - τ*)	-384.80	10.69	0.95
C_{max}	-26.43	0.73	0.91
C_{min}	-7.60	0.23	0.87

*τ = 24 hours

RAW DATA



SUMMARY OF RESULTS
SECTION 2.0: DAY 7 RAW (NON-NORMALIZED)
PLASMA DESACETYLDILTIAZEM

Mean Pharmacokinetic Parameters for Raw Plasma Desacetyldiltiazem
(n=23)

Parameter	Biovail ER (A) 1 x 120 mg Arithmetic Mean (%CV)	Biovail ER(B) 1 x 240 mg Arithmetic Mean (%CV)	Biovail ER (C) 1 x 300 mg Arithmetic Mean (%CV)
AUC (0 - τ^*)(ng·hr/mL)	143.37 (170.34)	369.90 (189.82)	462.39 (170.15)
C_{max} (ng/mL)	8.08 (175.64)	18.40 (169.63)	23.47 (151.50)
C_{min} (ng/mL)	5.07 (166.73)	13.38 (213.00)	15.85 (183.30)
T_{max} (hours)	12.04 (28.04)	11.48 (35.42)	12.13 (28.26)
Degree of Fluctuation (%)	47.49 (53.53)	47.78 (60.75)	49.06 (48.58)

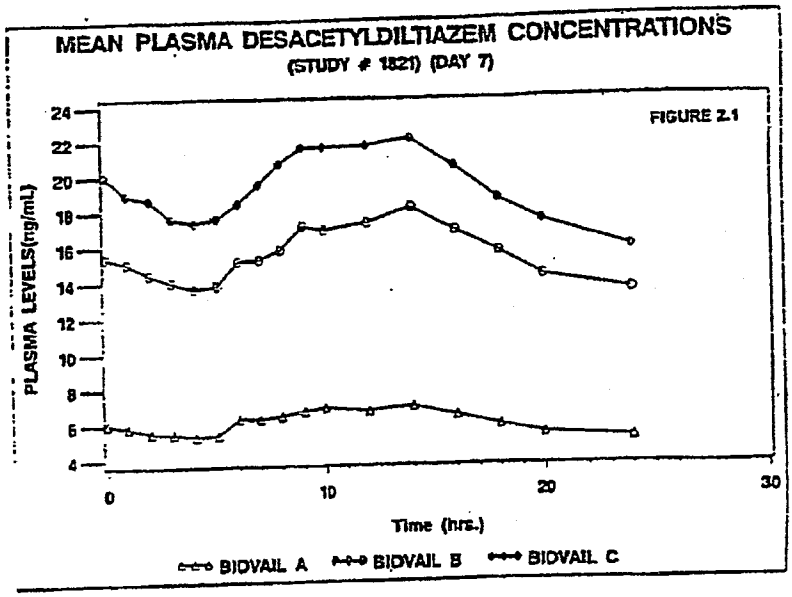
*τ = 24 hours

Linear Regression Analyses

	Intercept	Slope	r^2
AUC (0 - τ^*)	-68.31	1.79	0.96
C_{max}	-2.18	0.09	0.94
C_{min}	-2.03	0.06	0.89

*τ = 24 hours

RAW DATA



SUMMARY OF RESULTS
SECTION 3.0: DAY 7 RAW (NON-NORMALIZED)
PLASMA DESMETHYLDILTIAZEM

Mean Pharmacokinetic Parameters for Raw Plasma Desmethyldiltiazem
(n=23)

Parameter	Biovail ER (A) 1 x 120 mg Arithmetic Mean (%CV)	Biovail ER(B) 1 x 240 mg Arithmetic Mean (%CV)	Biovail ER (C) 1 x 300 mg Arithmetic Mean (%CV)
AUC (0 - τ*)(ng·hr/mL)	372.35 (21.94)	798.90 (22.56)	1003.02 (18.83)
C_{max} (ng/mL)	21.21 (24.51)	44.22 (25.55)	55.10 (19.48)
C_{min} (ng/mL)	5.07 (166.73)	13.38 (213.00)	15.85 (183.30)
T_{max} (hours)	11.83 (24.01)	12.52 (22.83)	12.48 (17.40)
Degree of Fluctuation (%)	63.09 (40.22)	58.21 (37.42)	60.37 (33.95)

*τ = 24 hours

Linear Regression Analyses

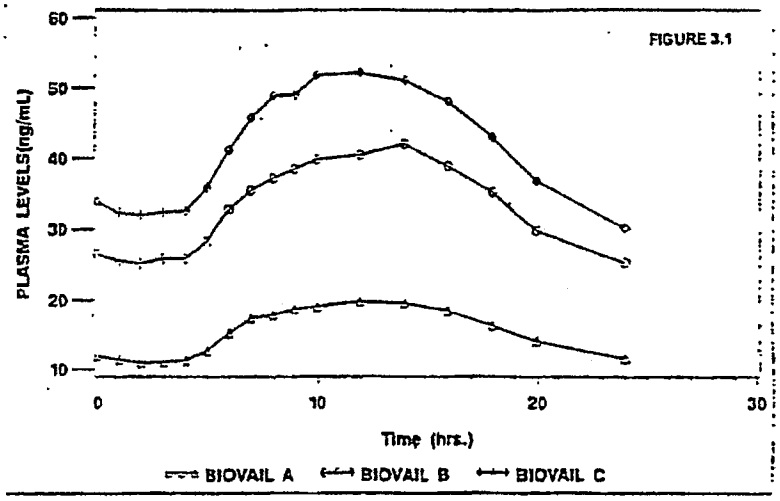
	Intercept	Slope	r^2
AUC (0 - τ*)	-47.65	3.51	0.98
C_{max}	-1.35	0.19	0.95
C_{min}	-0.77	0.10	0.94

*τ = 24 hours

RAW DATA

MEAN PLASMA DESMETHYLDILTIAZEM CONCENTRATIONS
(STUDY # 1821) (DAY 7)

FIGURE 3.1



IN THE UNITED STATES PATENT OFFICE

In re application of:

Kenneth S. Albert and Paul José Maes

Serial No. : 09/567,451 Our Ref. : PT1830000
Group Art Unit : 1615 CUSTOMER NO. 23607

Filed : May 8, 2000 Examiner : Amy E. Pulliam

For : CHRONOTHERAPEUTIC DILTIAZEM FORMULATIONS AND THE ADMINISTRATION THEREOF

REQUEST FOR EXTENSION OF TIME IN RESPONSE TO OFFICE ACTION

The Honorable Commissioner of Patents
UNITED STATES PATENT OFFICE
2011 South Clark Place
Crystal Plaza 2, Room 1B03
Arlington, Virginia 22202
U.S.A.

Dear Sir:

It is respectfully requested that the time for filing a response to the Office Action of May 25, 2001, now set to expire August 25, 2001, be extended for three months, to and including **November 25, 2001.**

Enclosed herewith please find a check in the amount of **$920.00 US** in payment of the three-month extension of time fee for a large entity. If there is any deficiency or surplusage of the fees enclosed, please obtain any such deficiency from or credit the surplusage to Deposit Account No. 08-3255 and advise Applicant's Agent.

Respectfully submitted,

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